Alcohol
Health effects

This document presents the summary and recommendations of the group of experts compiled by Inserm as part of a collective expertise procedure in order to respond to questions on the effects of alcohol consumption on health, raised by the Comité Français d'éducation pour la santé (CFES) (the French Health Education Committee), the Caisse nationale d'assurance maladie des travailleurs salariés (Cnamts) (National Health Insurance Scheme for Salaried Employees) and the Mission interministérielle de lutte contre la drogue et la toximanie (Mildt) (Interministerial Mission against Drugs and Drug Addiction).

The Centre d'expertise collective de l'Inserm (Inserm Collective Expertise Centre) has co-ordinated this collective expertise strategy with the Département animation et partenariat scientifique (Daps) (Leadership and Scientific Partnership Department) for the preparation of this dossier in conjunction with the Service de documentation du Département de l'information scientifique et de la communication (Disc) (Documentation Service of the Scientific Information and Communication Department) for the bibliographical research.

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Foreword

Today, the effects of alcohol on human health are still taking their toll in public health terms. According to the Comité français d'éducation pour la santé (CFES), 5 million people residing in France are estimated to have medical, psychological or social problems associated with excessive alcohol consumption.

Chronic alcohol intoxication triggers a high morbidity and mortality rate due to cancer, liver disease, adverse effects on the central or peripheral nervous system, cardiovascular diseases or abnormal development in children exposed *in utero*. Nevertheless, the consequences of alcohol intake on health depend on individual consumer susceptibility, on its pattern and, above all, its level of consumption.

In France, for most men and women, the consumption of alcoholic beverages (wine, beer, spirits and the like) is an intrinsic aspect of dietary or cultural habits, and the majority of individuals have no specific problem associated with this intake of alcohol. Recent epidemiological data even suggest a link between a moderate alcohol consumption and a lower mortality rate. The most significant association is generally observed after the age of 50 in industrialised countries where a high incidence of cardiovascular diseases is observed. There is, however, no evidence to substantiate a cause-effect relationship.

The Caisse nationale d'assurance maladie des travailleurs salariés (Cnamts), the CFES and the Mission interministérielle de lutte contre la drogue et la toxicomanie (Mildt), key players in policies for the prevention of alcohol consumption, wanted to question Inserm through the collective expertise procedure to obtain the most recent, scientifically validated data concerning the effects of alcohol on health in order to inform the population of the risks associated with the various levels of consumption and to better target messages relating to prevention. In order to meet this objective, Inserm brought together a multidisciplinary group of experts in the fields of epidemiology, biology, drug addiction and clinical signs of various diseases associated with excessive alcohol consumption.

The expert group considered the following questions:

- What is the fate of alcohol in the body? How can various biological (sex, age, weight, genetic inheritance) or environmental (food, level of exposure) parameters affect the toxicokinetics of alcohol?
- What are the effects of acute or chronic alcohol consumption on the central and peripheral nervous systems and on cognitive functions? What are the mechanisms of neurotoxicity?
- What are the consequences of *in-utero* exposure on foetal (teratogenicity, foetotoxicity) and child development? What mechanisms are involved in foetal lesions?
- What is the liver toxicity of alcohol? What are the mechanisms of action (cytokines, oxidative stress, etc.)?
- What is the impact of alcohol consumption on cardiovascular risk factors and on morbidity and mortality rates? What is the dose-effect relationship?
- What cancer risks are associated with alcohol consumption?
- What are the individual genetic susceptibilities to alcohol-related diseases?
- What is the relationship between alcohol consumption and nutritional status and corpulence?

Over 1 500 articles were selected after searching through international bibliographic databases. During the seven working sessions organised between November 2000 and May

2001, experts presented a critical analysis and a summary of the international studies published on the various effects of alcohol consumption. The last three sessions focused on drafting the main conclusions and recommendations. Lastly, papers were presented on the contribution of anatomical and functional medical imaging to the understanding of lesions associated with alcohol consumption and data on mortality due to severe chronic alcoholism.

Summary

Alcohol is a non-essential nutrient. The consequences of alcohol consumption on health vary according to the extent and habits of usage (excessive or not, acute or chronic), and depend on numerous environmental and individual factors. The methods used to investigate these effects will vary in adolescents, young adults and the elderly.

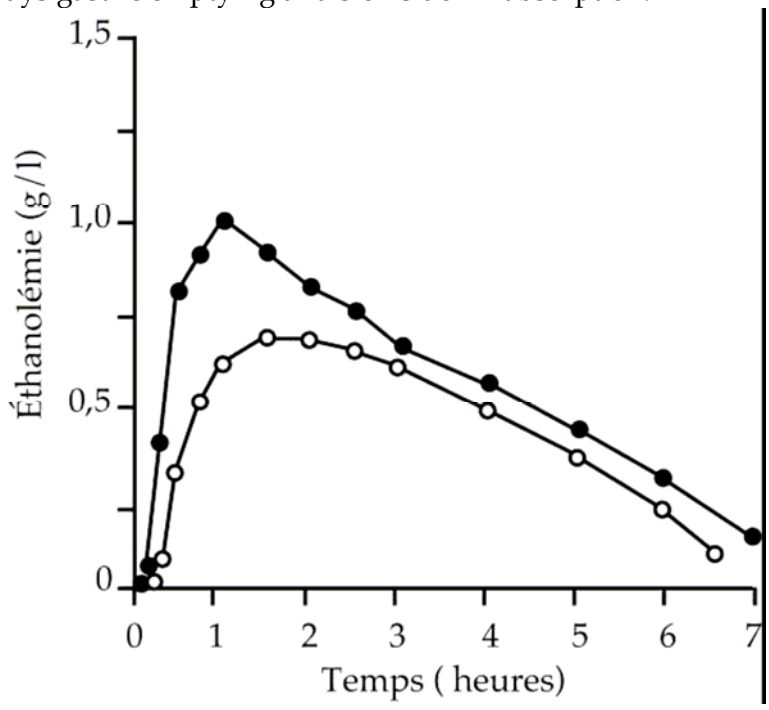
Since no intervention study can be envisaged in order to examine the long-term effects of alcohol, only prospective epidemiological studies conducted in representative populations can provide information. The reliability of the results of these studies will depend largely on the accuracy of the information collated in relation to alcohol consumption. These data are based on the declaration of individuals or informants, since there is still no biological markers to reflect real alcohol consumption.

The definition of one unit of alcohol varies from one region in the world to another, but it is generally recognised that one glass of beer (250-300 ml), one glass of wine (150 ml) and one measure of spirits (30-50 ml) contain a similar quantity of alcohol, averaging 10 g of pure ethanol. Consumption is usually reported on a "daily" or "weekly" basis.

Most studies have been conducted in Anglo-Saxon populations whose average alcohol consumption seems to be relatively low compared with that observed in the Latin countries. In surveys carried out in Italy and France, the "small" or "occasional drinkers" serve as a reference and not abstinent subjects who are more difficult to find. Furthermore, the method of consumption differs amongst the countries. Alcohol is consumed regularly in the Latin countries and mostly at the weekend in Anglo-Saxon countries. The fact that one particular type of drink (wine, beer or spirits) could be more "risky" or "protective" than the others is still open to debate. However, when similar results are obtained in studies carried out in populations who usually consume different drinks, then it is highly likely that the key factor is ethanol. However, so as not to attribute an effect triggered by other factors to ethanol, the so-called "confusion" factors must be adjusted statistically. This adjustment is thus an important element for consideration in the studies. Moreover, certain factors may interact, and this should be identified.

Most of the alcohol ingested enters the blood circulation.

Ethanol is a small molecule (CH_3CH_2OH) that is absorbed by simple diffusion. Slow in the stomach, this absorption process mainly (70% to 80%) takes place in the intestine (duodenum and jejunum). The ingestion of food slows down gastric emptying by closing the pyloric loop and reducing gastric motility, particularly in the antral region. The absorption kinetics of ethanol are modified by prolonging the contact time of ethanol in the stomach. A peak ethanol concentration in the plasma (in the blood) is obtained within 45 minutes if the subject has fasted, and within 90 minutes when the alcohol is ingested with food. In this case, the delayed peak is also lower and a smaller quantity of alcohol actually reaches the systemic circulation. Strong alcohols, i.e. those with a concentration exceeding 20%, trigger pyloric spasm, which delays gastric emptying and slows down absorption.



Absorption pharmacokinetics of ethanol on an empty stomach or after food (according to Lands, 1998). Values recorded in a man who consumed 0.80 g of alcohol/kg of body weight before (●) or after (❍) breakfast

Following absorption, ethanol is distributed to the highly vascularised organs such as the brain, lungs and liver within minutes (the distribution half-life is 7 to 8 minutes. The concentrations very quickly reach steady state levels in the blood. Ethanol is soluble in free body water without binding to plasma proteins. Its solubility in fats and bones is negligible. The respective proportions of lean mass (in which ethanol is distributed) in relation to the fat mass determine the distribution volume of ethanol. This volume averages 0.50 l/kg in women and 0.65 l/kg in men. Ethanol readily diffuses through the placenta and the concentrations recorded in the amniotic fluid and foetus are quite similar to the maternal plasma concentrations.

Ethanol is eliminated according to two mechanisms: it is either excreted or is metabolised by oxidation into acetaldehyde and then into acetate. It is eliminated unchanged in expired air, urine and sweat. The contribution of these various routes of elimination varies depending on plasma concentrations and the clearance values are low. Blood ethanol levels are estimated

from pulmonary elimination, based on concentrations in the expired air. Approximately 3% to 5% of the total quantity absorbed will be eliminated unchanged by the kidneys. Ethanol is excreted in breast milk at concentrations approximately 10% higher than those recorded in plasma. This is due to the fact that milk contains more water.

Ethanol is chiefly metabolised in the liver but other tissues may be involved in its oxidation. Ethanol undergoes a so-called "first-pass effect", i.e. a fraction is metabolised before reaching the systemic circulation. This initial metabolism occurs in the digestive mucosa and liver. The first-pass effect tends to involve no more than 20% of the dose of ethanol ingested. Over 80% of the alcohol ingested therefore penetrate the systemic circulation in the form of ethanol and are subsequently metabolised in the liver.

The elimination of ethanol at concentrations exceeding 0.50 g/l may be assimilated to a line, the rate being approximately 0.15 g/l/h, with significant inter- and intra-individual variations. The kinetics is, however, more complex in reality and can be modelled by the Michaelis-Menten equation.

The pharmacokinetic profile of ethanol differs in men and women. In view of the greater fat mass in women, the volume of distribution of ethanol in the lean mass is lower (0.50 g/l/kg) and triggers higher ethanol levels in the blood for the same quantity ingested. Recent studies have also shown that an isoenzyme (χ-ADH), which is involved in the gastric metabolism of ethanol (first-pass effect), is less active in women. This metabolism is consequently reduced for drinks containing between 10% and 40% of ethanol (but not for drinks containing 5% of ethanol). The pharmacokinetic profile also varies with age since the distribution between fat and lean mass changes in men and women over time: between the ages of 25 and 60, the fat mass doubles in men and increases by 50% in women.

Some drugs alter the pharmacokinetics of ethanol. Thus, molecules that accelerate gastric emptying (anti-emetics, travel sickness medication) advance the onset of peak blood ethanol levels whereas drugs that slow down the opening of the pylorus (anticholinergics) delay it. Gastric ulcers can be treated with histamine H2 receptor inhibitors, which are likely to inhibit the ADH in the gastric wall and thus to diminish the first-pass effect. The consequences of this ADH inhibition remain controversial *in vivo*.

Just as medicines can affect the pharmacokinetics of ethanol, ethanol can interact with the pharmacokinetic profile of medicines. The most significant interactions are observed during metabolism in the liver. The cytochrome, P450 2E1 (CYP2E1), the synthesis of which is ethanol-induced, also metabolises certain medicines such as paracetamol, analgesics and antipyretics (with hepatotoxic metabolite) that are widely prescribed and purchased over the counter. Under normal circumstances, this metabolite is detoxified by gluthathion conjugation. When CYP2E1 is induced, production of the toxic metabolite increases and the detoxification capacity of glutathion may be exceeded. In cases of chronic alcoholism, severe hepatitis, culminating in death in 20% of cases, may occur at barely supratherapeutic dose levels of paracetamol.

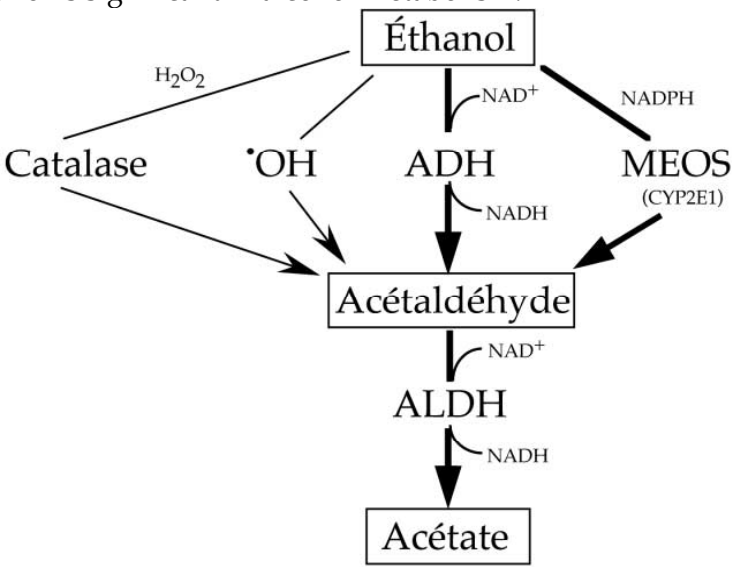
Ethanol is mainly metabolised in the liver.

Most of the ethanol ingested is oxidised into acetaldehyde and then into acetate in the liver. The most well-known metabolic pathways are those of alcohol-dehydrogenase (ADH) and the microsomal ethanol oxidizing (MEOS), which involves CYP2E1. The catalase pathways (that warrant the presence of hydrogen peroxide) and free radicals (oxidation of ethanol by the $^{\bullet}OH$ hydroxyl radical) are minor. Acetaldehyde is oxidised into acetate by aldehyde dehydrogenase (ALDH). Large quantities of acetate are released in the systemic circulation

and oxidised into CO_2 and H_2O in the extra-hepatic tissues.

ADH is a cytosolic, NAD-dependent enzyme that plays a crucial role in ethanol metabolism. It belongs to a polygenic group in which 7 genes (*ADH1* to *ADH7*) can be identified with polymorphic loci in the case of *ADH2* and *ADH3*. ADH genes are coded for the different sub-units, which are linked by two to form isoenzymes that are allocated to 5 classes depending on their enzymatic properties and sequence similarities.

Class I isoenzymes (α, β, γ sub-units) are found in copious quantities in the liver and have a marked affinity for ethanol (Km=0.002 to 0.200 g/l for common alleles). Together with the class II ADH, they play a very important role in the hepatic metabolism of ethanol is significant in alcohol metabolism.



The hepatic metabolism of ethanol

ADH regulation has been investigated in animals: fasting, a low calorie diet or zinc deficiency diminish its activity while corticosteroids, hypophysectomy, thyroidectomy, orchidectomy, glucagon and growth hormones have the opposite effect. Lastly, ADH activity is decreased in subjects who consume alcohol to excess and is increased following withdrawal.

ADH classification

Class	Gene	Allele	Sub-unit	Km ethanol [mM g/l)]		Vmax (min^{-1})	Tissue site
I	*ADH1*	*ADH1*	α	4,4	0.2	23	Liver,
	ADH2	*ADH2*1*	β1	0,05	0.002	9	liver lungs,
		*ADH2*2*	β2	0,94	0.04	340	liver, stomach
	ADH3	*ADH2*3*	β3	34	1.56	320	
		*ADH3*1*	γ1	1	0.05	88	
		*ADH3*2*	γ 2	0,63	0.029	35	
II	*ADH4*	*ADH4*	π	34	1.56	20	Liver
III	*ADH5*	*ADH5*	χ	1 000	46		All tissues (including the brain)
IV	*ADH7*	*ADH7*	σ,μ	37	1,7	1 510	Oesophagus, stomach
V	*ADH6*	*ADH6*	Unidentified	?	?	?	Liver

The kinetic constants are given for the dimers. Km (Michaelis constant) represents the alcohol concentration at which the enzyme functions at half of its maximum speed. Vmax represents the maximum speed of enzymatic activity and is expressed in mole of substrate metabolised per minute and per mole of enzyme. The enzymes work at top speed for concentrations of approximately 10 to 20 Km.

Chronic alcohol consumption and the ingestion of high dose levels (blood alcohol level exceeding 0.5 g/l) involve CYP2E1, which belongs to the cytochrome P450 super family.

This is a predominantly hepatic, NADPH-dependent enzyme. Its major characteristic is that it can be induced by alcohol but has a very short half-life (7 to 37 hours). Responsible for approximately 10% of the metabolism of ethanol in the non-induced state, its activity is increased between 5- and 10-fold in excessive alcohol consumers, the rate of ethanol elimination thus being increased by 10% to 20%.

Acetaldehyde is oxidised into acetate by ALDH, a NAD-dependent enzyme belonging to a super family comprising 16 genes in man. Two isoenzymes, namely ALDH1 and ALDH2, are involved in alcohol metabolism: ALDH1, which is cytosolic, possesses variants that explain the varying individual sensitivity to ethanol but the molecular basis for these differences has not been elucidated. ALDH2, which is mitochondrial, has a much stronger affinity for acetaldehyde than ALDH1 and is mainly responsible for the oxidation of acetaldehyde into acetate. Genetic polymorphism resulting in a totally inactive enzyme has been described in Asians in conjunction with the mitochondrial ALDH. Excessive alcohol consumption reduces ALDH activity in man.

In the liver, ethanol oxidation mainly triggers an increase in the $NADH/NAD^+$ ratio, which, in turn, disrupts carbohydrate and lipid metabolism. Fatty liver, which develops in subjects who consume alcohol to excess, is one such example: the increase in the $NADH/NAD^+$ ratio inhibits the β-oxidation of fatty acids and promotes the accumulation of triglycerides in the liver. Acetaldehyde, a highly toxic metabolite for the liver since it is extremely reactive, is capable of forming adducts to adjacent molecules (enzymes and other proteins &ldots;). This alters their properties, possibly rendering them incapable of exerting their activity on the one hand, and antigenic on the other. These consequences are, nevertheless, limited by maintaining very low concentrations of acetaldehyde metabolised into acetate by ALDH. Ethanol-induced CYP2E1 triggers an increase in the production of free radicals, which tends to play a part in the onset of liver disease. Free radicals, which cause lipid peroxidation, are thus involved in the structural disorganisation of cell membranes. CYP2E1 can also activate certain xenobiotics (organic solvents and paracetamol, etc.) into hepatotoxic agents and certain procarcinogenic substances (nitrosamines, etc.) into carcinogens, thus accounting for the hepatotoxicity of certain xenobiotics or the development of some forms of cancer in consumers of excess alcohol.

The liver is one of the principal targets for the effects of alcohol

Almost 9 000 (8 863) deaths due to alcohol-induced cirrhosis of the liver were recorded in France in 1998. This figure has been stable since the 1990s following a marked decrease from the 1970s onwards. Half of these deaths occur between the ages of 45 and 64.

The *sex ratio* of almost 3 men to 1 woman in 1998 should be compared against that recorded in excessive drinkers, which is estimated to be around 4 men to 1 woman. The mortality data therefore confirm the extreme severity of the disease in women. Finally, there is a marked geographical disparity with a cirrhosis-induced mortality gradient decreasing from north to south, the mortality rate being 3 times greater in men and almost 5 times greater in women

in the Nord-Pas-de-Calais region than in the Southern-Pyrénées region.

Liver diseases caused by excessive alcohol consumption (fatty liver, alcohol-induced hepatitis and cirrhosis) can occur either individually or concomitantly. They are difficult to diagnose. Apart from in the case of cirrhosis and severe alcohol-induced hepatitis, the clinical signs are inconclusive. Laboratory findings are often disrupted but their contribution to the diagnosis is evident only in binary mode (liver disease/no liver disease) without providing any reliable information regarding the type of lesions involved. Only histological analysis of the liver will elicit an accurate diagnosis: a liver biopsy must be performed (intercostal biopsy under local anaesthesia) warranting hospital admission. Despite its essential interest in the diagnosis of alcohol-induced liver disease, histological examinations are rarely performed, even in consumers of excess alcohol who have been admitted to hospital.

Given the lack of diagnostic precision, the real prevalence of alcohol-induced liver diseases and their natural history is misunderstood. A French study performed in a group comprising over 2 000 excessive alcohol consumers admitted to hospital with modified results in liver laboratory tests showed that 34% of these subjects presented with alcohol-induced cirrhosis, 46% with fatty liver with/without fibrosis, 9% with acute alcohol-induced hepatitis and 11 % with a normal liver. Based on an analysis of all the published data, cirrhosis occurs in approximately 20% of hospitalised excess alcohol consumers. Some factors promote the advance of alcohol-induced cirrhosis. Women are more sensitive to alcohol-induced hepatotoxicity; severe fatty liver affecting more than 50% of the hepatocytes increases the risk of development of the disease, possibly culminating in cirrhosis, by 7-fold. The existence of acute alcohol-induced hepatitis and the presence of fibrosis around the centrolobular veins are also contributing factors to this disease. Although an invasive technique, histology is a precious tool for diagnosis and prognosis in such cases.

It is difficult to establish the consumption threshold beyond which the risk of alcohol-induced cirrhosis increases substantially (risk multiplied by a factor of 3 to 4). On examination of published studies, it can be estimated that, in an individual devoid of any other risk factor, this threshold must be set at approximately 30 g of alcohol per day (3 glasses) in women and 50 g of alcohol (5 glasses) in man for periods of at least 10 and 15 years in women and men respectively. The influence of consumption habits (daily *versus* acute at the weekend, consumption on an empty stomach *versus* with food) on the risk of alcohol-induced liver disease and cirrhosis has yet to be specified. According to current data, it is impossible to associate a lower risk of alcohol-induced liver disease to one single type of drink. Malnutrition and obesity also appear to be risk factors in terms of alcohol-induced liver disease.

Alcohol consumption is a serious factor in the advance of chronic viral infections (hepatitis B and C) since it increases the rate and/or the speed of onset of cirrhosis and hepatocellular carcinoma. The prevalence of hepatitis B serum markers, which is strongly linked with the advance of liver cancer, is between 3 and 5 times greater in hospitalised excess alcohol consumers than amongst the general population, and even greater again in cases of concomitant liver cancer. The frequency of contamination due to the hepatitis B virus (VHB) in consumers of excess alcohol and the potential risk of active infections and liver cancer have led to the introduction of anti-VHB vaccination tests in excess alcohol consumers. The vaccine response rate in this population is correct apart from in the case of cirrhotic patients in whom the response rate is only around 50%. However, since anti-HBs antibody titres are low, the vaccine programme carried out is probably unsuitable for subjects who drink alcohol to excess.

Infection due to the hepatitis C virus (VHC) is also common in excess alcohol consumers,

around 10% of subjects being sero-postitive and up to 50% presenting with liver cancer. The infection is generally due to former intravenous drug addiction, alcohol consumption replacing that of heroin. All of the published results confirm the particularly harmful role of alcohol in the onset of VHC-related cirrhosis. In a study conducted in France in patients presenting with chronic VHC infection, the frequency of cirrhosis was 40% in subjects presenting with excessive alcohol consumption compared with 20% in moderate drinkers. Hepatologists therefore recommend very low alcohol consumption or even abstinence in VHC-infected subjects.

Alcohol-induced liver diseases are serious conditions because 5-year survival varies from 20% to 60% in cases of established cirrhosis and/or severe alcohol-induced hepatitis. Treatment is based on the ABC approach, ABC standing for *abstinence*, *bed rest* and *calories*. Nowadays, medication have only marginal impact; only corticosteroids have proved beneficial in the management of acute, severe, alcohol-induced hepatitis, improving the survival rate by 20%. Lastly, liver transplantation remains the ultimate strategy in cases of severe cirrhosis. Between 1988 and 1997, 3 335 transplantations due to alcohol-induced cirrhosis were performed in Europe. This condition accounts for slightly more than a quarter of transplantation indications. The post-transplantation survival rate of patients with alcohol-induced cirrhosis is similar to that observed with viral cirrhoses (70% survival at 3 years) and generally moderate alcohol consumption is resumed after transplantation in approximately 15% to 40% of subjects without any effect on transplanted organ survival.

Transplantation is currently proposed for all alcoholic patients presenting with severe cirrhosis, which does not improve after 6 months of total abstinence.

Oxidative stress is one of the essential mechanisms of ethanol-induced hepatotoxicity

Vast progress has recently been made in understanding the mechanisms involved in alcohol-induced liver diseases. Over time, alcoholism triggers liver conditions ranging from fatty liver (steatosis), hepatitis, hypoxia, necrosis and fibrosis, possibly culminating in cirrhosis. Current research endeavours to pinpoint the key stages in disease advance and to specify the therapeutic targets. The products of ethanol metabolism (NADH, acetaldehyde), reactive oxygen species (ROS) and cytokines are important aetiological factors.

The presence of oxidative stress in the liver, generally manifested in the form of exacerbated lipoperoxidation, is often detected under various conditions of experimental or human alcoholisation. The excessive production of ROS is largely responsible for this oxidative stress. Experimental ethanol administration increases the formation of oxygen-reduced derivatives ($O_2^{\bullet -}$ superoxide anion, H_2O_2 hydrogen peroxide) in the liver by different enzymatic systems with isoenzyme CYP2E1 appearing to play a crucial role. The biosynthesis of aggressive radical forms such as the hydroxyl radical ($^{\bullet}OH$) is catalysed by transition metals, especially iron. Numerous disruptions in liver metabolism have been observed following ethanol administration. The increase in active redox iron, which may result from excess iron stores in the cell or excessive iron release from storage proteins, at least in part, can be a decisive factor in the initiation and propagation of lipoperoxidation.

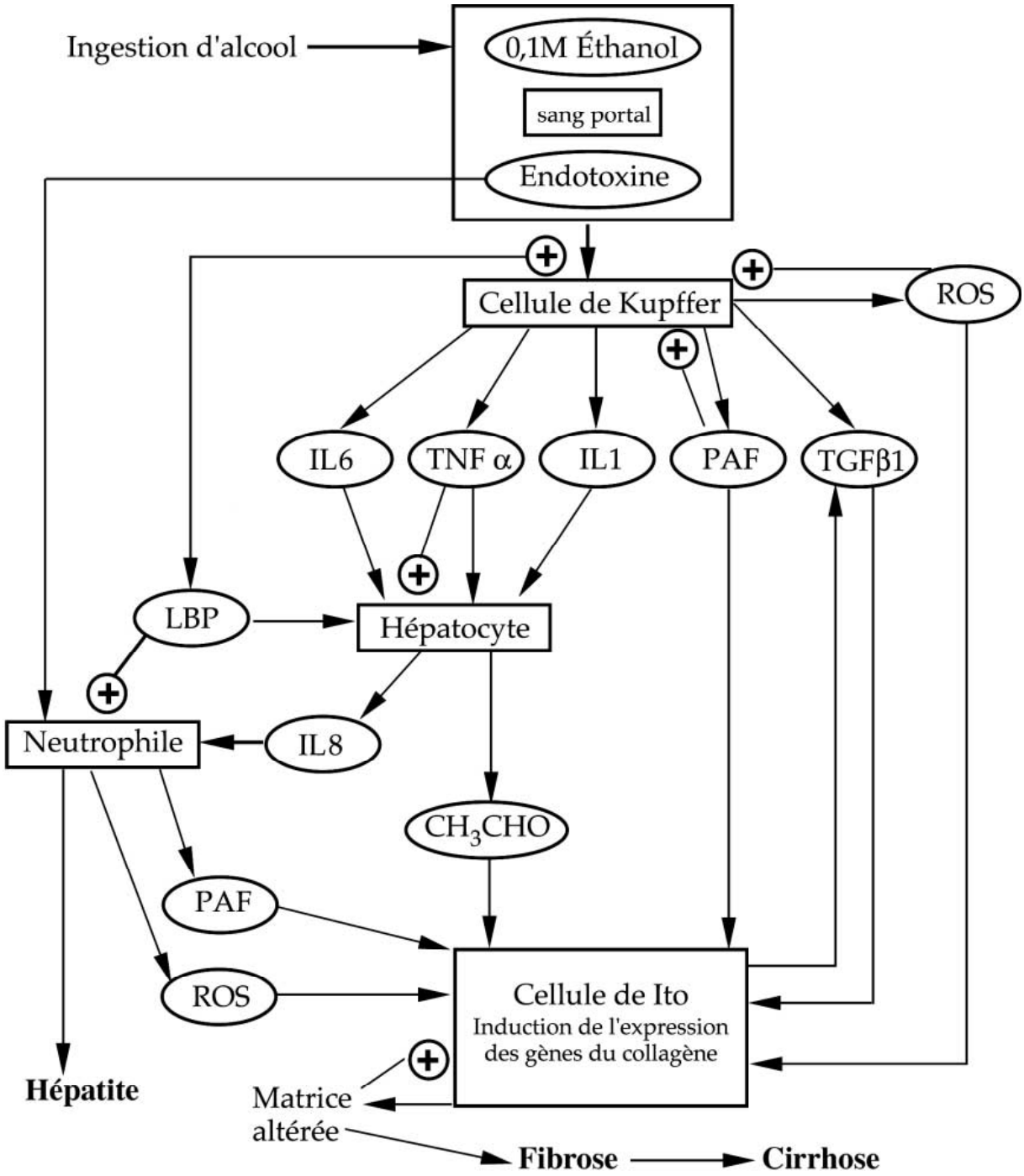
Cells possess a number of substrates and enzymatic systems that are involved in the antioxidant defence preventing ROS from altering the cell components. A reduction in the anti-oxidant defence, as manifested by the reduction in the activities of superoxide dismutase (SOD,Cu-Zn), glutathione peroxidase and substrates such as vitamin E and glutathione have often been described during alcoholisation.

The experimental study of the role of oxidative stress in ethanol-induced hepatotoxicity has benefited from the development of a murine alcoholisation model facilitating ethanol administration in conjunction with an hyperlipidic diet. This is the only model to trigger histological lesions similar to those observed during severe forms of liver disease in man (steatosis, inflammation, fibrosis and necrosis). These lesions are associated with CYP2E1 induction and with the stigmas of oxidative stress (high increase in lipoperoxidation and oxidative changes in proteins). There is a significant correlation between the pathological score (highlighting the severity of the anatomopathological alterations) and oxidative stress parameters . Furthermore, a diet enriched with polyunsaturated fatty acids and iron stimulates lipoperoxidation and exacerbates the liver lesions. These results indicate a causal relationship between oxidative stress and the extend of liver diseases.

Pro-inflammatory cytokines are involved in the pathogenesis of alcohol-induced liver lesions

Numerous experimental studies have highlighted the dominating role of cytokines in liver necrosis, endothelial lesions, the myofibroblastic transformation of hepatic stellate cells (Ito cells), the tissue recruitment of polynuclear neutrophils and, finally, activation of Kupffer cells. Four key factors motivated the investigation of cytokines during alcohol-induced liver disease: Some cytokines would be directly responsible for hepatocytic and clinical-biological signs observed during acute, alcohol-induced hepatitis; the activation, recruitment and migration of neutrophils circulating in the liver call for cytokine intervention; entotoxinaemia, often detected in consumers of excess alcohol, is associated with cytokine secretion in numerous diseases; last, but not least, some cytokines could be a preferential therapeutic target in patients suffering from alcohol-induced liver diseases.

In alcohol-induced liver disease, activation of Kupffer cells basically affects hepatic disease advance. In fact, a number of arguments plead in favour of the role of cytokines released by Kupffer cells in the inflammation process, apoptosis, necrosis and fibrosis. This activation is due to the action of various compounds and, in particular, to that of endotoxin of intestinal origin (lipopolysaccharide or LPS, forming the outer coat of Gram-negative bacteria) present in the portal vein following bacterial translocation. The Kupffer cells activated by the endotoxin synthesize and release numerous cytokines including TNF α (*tumour necrosis factor* α), IL1 (interleukin 1), IL6 and TGF β (*transforming growth factor* β) together with ROS and PAF (*platelet-activating factor)*. These factors initiate a cascade of reactions involving the various types of cell located in the liver (monocytes, neutrophils, Ito cells and endothelial cells), culminating primarily in the self-activation of Kupffer cells that perpetuate the inflammatory cycle.



Cytokines involved in alcohol-induced liver diseases (according to Lands, 1995). ROS: reactive oxygen species; CH_3-CHO: acetaldehyde; IL (1,6): interleukin; TNF: *tumour necrosis factor*; PAF: *platelet-activating factor*; TGF: *transforming growth factor*; LBP: *lipopolysaccharide binding protein*

Numerous experimental facts have confirmed the role of endotoxin in the origin of alcohol-related liver lesions. Endotoxinaemia is frequently detected in patients who consume excess quantities of alcohol and having histological liver lesions. Intestinal permeability to LPS is enhanced in these patients, particularly in the group presenting with liver lesions and in rats as from the fourth week of alcohol-based treatment. Acute alcohol administration increases the concentration of endotoxin in the portal vein. Antibiotic therapy or the ingestion of lactobacilli reduces the passage of endotoxin into the splanchnic circulation together with histological lesions and activation of Kupffer cells. Furthermore, there is a synergistic effect between the alcohol and the endotoxin.

Some cytokines released by the Kupffer cells, including TGFβ, exhibit fibrogenic effects by acting on perisinusoidal Ito cells. Activation of the latter is accompanied by their transformation into myofibroblasts, which express PDGF (*platelet-derived growth factor)* receptors on their surface, activation of which promotes cell proliferation. Moreover, TGFβ stimulates its own synthesis and that of procollagen and fibronectin. The Ito cells therefore develop gradual self-activation of the fibrogenic process. Acetaldehyde and the products of lipoperoxidation also stimulate this fibrogenic activity. The differentiation, proliferation and activation of Ito cells are thus involved in the changing physiology of the liver. A reduction in the severity of inflammatory and fibrous lesions can be obtained experimentally by administering gadolinium chloride during alcoholism. Gadolinium chloride is an agent that destroys Kupffer cells. This last observation corroborates the fundamental role of Kupffer cells in the initiation and extension of liver fibrosis.

Other compounds such as acetaldehyde, the products of lipid peroxidation, inflammatory cytokines, the transcription factor NFκB (*nuclear factor* κB) and iron are also involved in activating Kupffer cells. It must be noted that these activation factors mutually regulate each other. The transcription factor NFκB – a potent stimulator of regions promoting the genes of inflammatory cytokines (TNFα, IL6, IL8) and adhesion compounds (ICAM-1 *intracellular cell adhesion molecule*, VCAM-1 *vascular cell adhesion molecule*, E-selectin) - is itself activated by TNFα, acetaldehyde, iron and reactive oxygen species.

Alcoholism alters the functions of the mitochondria, which enhance its sensitivity to the signals of apoptosis or necrosis initiated by TNFα. The effects of TNFα on hepatic cells nevertheless largely depend on the modulation of the various signals released and the growth factor expression, the result of which may be apoptosis, necrosis, survival or cell proliferation. Although many studies show that TNFα plays a crucial role in alcohol-induced liver diseases, other factors act either synergistically with TNFα to trigger cytotoxic effects or else attenuate or neutralise its effects. The list of protection systems has not been clarified at the present time. A significant increase in serum TNFα levels can be seen, particularly in cases of cirrhosis and acute alcohol-induced hepatitis (AAH) in particular. The prognostic value of the TNFα level in severe forms of AAH has been assessed in four studies: a high level would be indicative of death. In these studies, however, the TNFα level was correlated with bilirubin, albumin and creatinine levels, thus suggesting that it could be a straightforward, indirect marker of the severity of AAH. The independent prognostic value of TNFα serum levels has been established in two series comprising a limited number of patients. TNFα enhances the expression of β2 integrins CD11a/CD18 and CD11b/CD18 receptors on the leukocyte surface, and that of ICAM1 (membrane ligand of β2 integrin) adhesion molecules on the surface of deficient hepatocytes. The expression of ICAM 1 adhesion molecules and β2 integrin receptors increases during alcohol-induced liver disease. This stimulation is involved in the migration and adhesion of neutrophils to hepatocytes during necrosis.

Given the various properties of IL8, particularly its chemotactic effect against polynuclear neutrophils, this cytokine has been studied during alcohol-induced liver disease. The plasma levels of IL8 in sufferers of acute alcohol-induced hepatitis are at

least twice those recorded in patients suffering from uncomplicated alcohol-induced cirrhosis. Mean IL8 serum levels fall prematurely during administration of prednisolone – a product used in the management of severe forms of AAH.

Defective anti-inflammatory cytokine secretion could also be involved in the pathogenesis of alcohol-induced liver disease. IL10 in particular has been widely studied, mainly due to its inhibitory effects on macrophages. The monocytes of patients presenting with alcohol-induced cirrhosis reveal defective IL10 secretion following *ex-vivo* stimulation by LPS. *In vitro*, the administration of anti-IL10 antibodies enhances the production of TNFα in the monocyte cultures of healthy subjects, but does not significantly modify TNFα production in the monocytes of patients suffering from cirrhosis. IL10 therefore inhibits TNFα in healthy subjects whereas defective IL10 secretion in cirrhotic patients could be involved in excessive TNFα production. Acute, severe, alcohol-induced hepatitis is also associated with defective anti-inflammatory regulation, as manifested by the high levels of IL8 and TNFα and the low levels of IL10. In the alcoholic rat model, severe histological impairment is accompanied by defective IL10 production and extensive TNFα synthesis. In this model, the administration of anti-TNFα or anti-CD18 antibodies triggers a fall in transaminase levels and improves hepatic lesions. Future clinical trials should assess the real benefit of pro-inflammatory cytokine inhibition in patients presenting with severe forms of alcohol-induced liver disease.

Ethanol is neurotoxic regardless of whether consumption is acute or chronic.

The neurotoxicity of ethanol can be considered in the form of functional toxicity (or acute effects) resulting from a single dose and lesion toxicity (or chronic effects) resulting from prolonged consumption. Functional toxicity is manifested by a series of disorders characterising acute alcoholic poisoning. Behavioural changes associated with alcohol consumption vary according to the dose ingested: psychostimulating effect for blood alcohol levels less than or equal to 0.50 g/l, a sedative effect being apparent beyond this value. The psychostimulating effect is accompanied by disinhibition: cognitive tasks are performed more quickly with a subjective sensation of ease but with an increased level of error. This disinhibitor effects leads mainly to a change in risk-taking behaviour, which helps considerably in explaining the risks associated with alcohol, not only when driving but also when carrying out multiple tasks. The frontal cortex – a region involved in carrying out cognitive tasks – has proved to be particularly sensitive to the effects of alcohol, which inevitably appear with blood alcohol levels of the order of 0.50 g/l, and probably at lower levels also. In fact, other factors in conjunction with blood alcohol levels are responsible for modifying behaviour, particularly consumption habits and individual variability.

In the long-term, alcohol consumption triggers disorders which, unlike acute effects, are not associated with the level of alcohol in the blood, and which may persist after abstinence of several months' or even several years' duration. Some complications (vascular, traumatic and metabolic, etc.) are indirect. Others are not due to alcohol consumption but to withdrawal, which may trigger delirium, hallucinations and epileptic seizures.

Peripheral neuropathies mainly affect the lower limbs and optic nerve and regress only slowly. Little progress has been made in recent years with regard to understanding and treating these conditions. Amongst central nervous system disorders, certain

encephalopathies may occur albeit rarely: Marchiafava-Bignami's disease, central pontine myelinolysis and pseudo-pellagra. Apart from central pontine myelinolysis, which is caused by sodium metabolism disorders, the mechanisms of these conditions are still unknown. They do not appear to be specific to alcohol poisoning.

Wernicke's encephalopathy, which, left untreated, is generally followed by Korsakoff syndrome, and mid-cerebellar syndrome, are frequent complications of alcohol poisoning. Initial recognition of Wernicke's encephalopathy combining a confused state of mind, ophthalmoplegia and ataxia, is important because disease advance to Korsakoff's syndrome (anterograde amnesia, temporo-spatial disorientation, fabrication and false recognition) is serious and the memory disorder can greatly disrupt the patient's social life. Wernicke-Korsakoff's syndrome can, however, be easily prevented by thiamine administration.

Less serious cognitive disorders are extremely common (affecting over 50% of cases) in alcohol-dependent patients. These disorders also have a socio-professional impact and can be reversed only slowly. They affect not only the memory (visual memory in particular), but also visuomotor and perceptive capacities and more elaborate functions such as praxis (performance of coordinated actions), abstraction or elaboration capacities. The similarity between these disorders and frontal involvement has been emphasised. Their link with Korsakoff's syndrome has been discussed (continuum theory), but these disorders appear to be triggered by a different mechanism.

There is no single mechanism to explain the neurotoxicity of alcohol. Ethanol itself is neurotoxic and numerous cell-related effects have been described. At high dose levels, alcohol disrupts the neurotransmission systems, inhibits catecholaminergic systems and excitatory amino acids, and activates the GABAergic system. In the course of alcohol intoxication, some changes can be highlighted with imaging techniques or during anatomo-pathological examination. These include reduced white matter, particularly in the corpus callosum, the cortex and the cerebellum, which is reversible; along with neuronal loss assumed to be irreversible, mainly in the prefrontal cortex, the hypothalamus and cerebellum.

Other indirect mechanisms also appear to be involved. However, only thiamine deficiency during Wernicke-Korsakoff 's syndrome has well documented. The white matter lesions observed in the course of this syndrome mainly affect the regions surrounding the 3rd ventricle, the hippocampus and the thalamus. These are initially haemorrhagic suffusions associated with glial proliferation. Neurotoxic effects could also be associated with the repetition of untreated withdrawal syndromes during which mechanisms of excitotoxicity related to excess glutamate have been involved. Epileptic activities are more common in patients having experienced repeated withdrawal syndromes.

Although the mechanisms of alcohol-induced neutrotoxicity are still uncertain and probably manifold., the effects seem to be observed only in persons whose daily alcohol consumption exceeds WHO-recommended limits (three glasses in men). It is, however, extremely difficult to set a precise threshold. In fact, there is nothing to indicate that the threshold would be the same for the various neurological complications associated with alcohol consumption.

The addictive potential of ethanol, which has now been established, can also be considered as a neurotoxic effect.

Cerebral imaging techniques reveal anatomical and functional abnormalities in chronic alcohol consumers.

The brain pathophysiological mechanisms involved in alcoholism have been investigated using imaging techniques to study brain morphology and functional activity. Scanning has highlighted the presence of global cortical atrophy and ventricular dilatation in chronic alcoholics. These conditions are partly reversible following withdrawal The correlations with neuropsychological tests are inconsistent. Scanning has also confirmed more specific involvement of the frontal lobe and diencephalic regions, these abnormalities being better correlated to cognitive deficiencies. Magnetic resonance imaging studies (MRI) in chronic alcoholics suggest that the cerebral water content is reduced during inebriation and increases on abstinence.

In functional imaging, reduced cerebral blood flow has been reported most frequently in the grey matter and, more rarely in the white matter. This effect on the grey matter could be associated with the direct neurotoxic effects of alcohol. Furthermore, an investigation of the glucose consumption reflecting functional activity in the various cerebral structures, revealed diminished activity in the mediofrontal and mid-cerebellar region consistent with the extent of neurological involvement. Confined, frontal dysfunction could, however, appear even in the absence of neurological complications. These metabolic abnormalities may be associated with the neuropsychological and behavioural disorders of chronic alcoholics. After 1 to 2 months of abstinence, the global metabolism of all cortical regions, of the cerebellum, thalamus and hippocampus reverts to virtually normal values.

Studies have highlighted changes in neuronal activity in alcoholics with more marked alterations in certain regions. It seems that the dopaminergic route could be altered during alcohol poisoning. Reduced ligand binding to dopaminergic receptors was thus shown experimentally. A reduction in the binding capacity of serotonin, which depends on the duration of intoxication, was also observed in patients consuming excessive quantities of alcohol compared with healthy subjects.

The fetal central nervous system is particularly sensitive to maternal alcohol consumption during pregnancy.

The alcohol ingested by pregnant women easily diffuses through the placenta and concentrations are rapidly balanced between the mother and child. Depending on the mother's drinking habits, her metabolic capacities and individual fetal sensitivity, the disruptions likely to be observed exist along a continuum, ranging from minor behavioural disorders to severe abnormal development indicative of « fetal alcohol syndrome» (or FAS) characterised by craniofacial dysmorphia, growth retardation and behavioral and cognitive handicaps.

The development of all organs can be affected by prenatal exposure to alcohol but the specific profile of the brain development, which continues throughout pregnancy and after birth, makes the central nervous system the principal target of alcohol-mediated effects. In this way, craniofacial dysmorphia observed under FAS conditions would be due to anomalies in primary structures of the brain, and particularly of the neural crest, caused by exposure to alcohol during the first month of pregnancy. During the second month, alcohol modifies the cells' ability to respond to regulatory elements such as growth factors and alters neuronal proliferation. By virtue of its effect on guide cells, i.e. radial glial cells, alcohol also impairs neuronal migration, resulting in the presence of ectopic cells in various cortical regions. Lastly, the active phase of cerebral growth, which occurs during the third trimester of pregnancy, is disrupted by alcohol, which destroys certain neurones, delays myelination and affects the process of synapse formation.

Studies conducted in animal models, especially in rats, have revealed a good correlation between brain anatomical alterations and the neurological deficits observed as a result of *in-utero* exposure to alcohol. In particular, the extent of the lesions affecting the hippocampus – the principal structure involved in learning and memory processes – reflects the cognitive disorders detected in children whose mothers consumed alcohol during pregnancy. Similarly, delayed motor growth and the difficulties encountered in executing sophisticated motor tasks are consistent with the reduction in the size and number of cerebellar cells that support this type of capacity.

Numerous systems have been shown to be affected by prenatal exposure to alcohol. Neuro-mediators such as glutamate, GABA (γ-aminobutyric acid) or dopamine play a decisive neurotrophic role during cerebral development. They regulate nerve cell differentiation and are involved in the formation neuronal networks. In the fetal brain exposed to alcohol, all of these neuromediator systems are disrupted, both in terms of structural aspects (receptors and uptake sites, etc.) and functional properties (changes in receptor affinity, modifications to the systems for transducing synaptic messages, etc.). Furthermore, it would appear that premature exposure to alcohol tends to shift the neurotransmission balance by reducing stimulating capacities, chiefly mediated by the glutamatergic system, in favour of inhibitory systems such as those regulated by GABA. In the respect, a certain number of cell losses observed under the effect of alcohol have been attributed to inappropriate stimulation of the physiological programme of cell death (apoptosis), probably secondary to functional deficits of NMDA (*N*-methyl-D-aspartate) glutamate receptors subtypes.

Fetal exposure to alcohol is also likely to disturb the action of growth factors (such as IGFs, *Insulin-like growth factors*) and hormonal systems that influence brain development. An important role has been attributed to the harmful effects of alcohol on the availability of retinoic acid, which, after binding to its receptors, acts as a transcription factor regulating the expression of numerous genes directly involved in embryogenesis and nerve cell differentiation.

Many arguments suggest that oxidative stress is involved in the adverse effects of alcohol on brain development inasmuch as fetal tissue is particularly sensitive to this type of aggression. Lastly, the harmful effects of alcohol *in utero* are likely to be increased by the disrupted nutritional status of an alcohol-consuming mother, wich is known to trigger a reduced intake of anti-oxidant compounds.

Thus, it is now clearly documented that the fetus is exposed to many risks following maternal alcohol consumption during pregnancy. These risks are particularly dangerous for the development of the central nervous system, which is largely devoid of repair capacities. In animals, the harmful effects of alcohol exposure can vary depending on the pattern of maternal alcoholisation. Alcohol absorption is, however, dangerous throughout pregnancy, and a threshold dose under which there are no risks to the offspring has never been established.

Alcohol consumption during pregnancy can impact upon the child's psychomotor development.

Fetal alcohol syndrome (FAS) was first described in 1968. The diagnosis is based on a combination of signs observed in children born to mothers who consume alcohol to excess. These signs may manifest as delayed pre- or post-natal growth, central nervous system abnormalities: neurological anomalies, delayed intellectual development, behavioral disorders, altered intellectual functions and/or structural anomalies [such as microcephaly

(cranial perimeter < 3rd percentile) or brain malformations detected by imaging techniques or at autopsy], facial characteristics with minor craniofacial anomalies including narrow eyelids, an average-sized elongated face, an indistinct philtrum and a thin upper lip. There is also a higher frequency of other non-specific, congenital malformations, especially cardiac, skeletal and muscle tissue defects. The major problem concerning the future development of these children is the effect on the central nervous system. Almost one child in every two affected by FAS is mentally retarded (IQ < 70), and most present with learning, memory, attention or behavioral disorders.

FAS does not affect not all children born to women who consume excessive amounts of alcohol: genetic, nutritional or environmental factors could intervene in the aetiology of this syndrome. There is a continuum of anomalies and some children who have been exposed prenatally to alcohol may have central nervous system defects without any facial changes or FAS-induced retarded growth.

The incidence of this syndrome (number of cases per 1 000 births) is difficult to determine, mainly due to the diagnostic difficulty based at birth on craniofacial anomalies and retarded growth. Moreover, estimations differ according to the geographical region in question and therefore depend on female alcohol consumption levels. The incidence is estimated at 0.5-3.0 per 1 000 births with higher levels being recorded in some populations. A study conducted in Roubaix between 1986 and 1990 quotes an incidence of 2.3 per 1000.

There is no doubt as to the teratogenic potential of high levels of alcohol. The effects on children of exposure to lower doses than those triggering foetal alcoholisation syndrome are less well understood. Women of child-bearing age consume less alcohol than men. When they are pregnant, most women reduce their alcohol consumption, generally as from the first trimester of pregnancy. In the perinatal survey conducted in 1995 in all French maternity hospitals (representative sample), 5 % of the women interviewed at the hospital declared that they drank at least one glass of alcohol per day during their pregnancy; in 1998, this percentage was 3.9 %. Similarly, a study carried out at the Roubaix Maternity Hospital confirmed a lower declared consumption rate in pregnant women: 15 % of the women drank at least 2 glasses per day in 1985-1986, compared with 10 % in 1990-1991 and 4 % in 1992.

Excessive alcohol consumption affects female fertility. In men and women, moderate alcohol intake is not associated with reduced fertility. An increased perinatal mortality or prematurity has been observed in certain studies in cases where about two glasses/day were consumed but the confounding factors are not always checked. The birth weight is, on average, lower for children exposed *in utero* to average or high alcohol levels. The results are less marked for lower exposures (less than 2 glasses per day), some studies showing differences for the consumption of one glass/day and others not observing any effect under the consumption of 3 or 4 glasses/day. Therefore, no threshold under which there would be no impact on birth weight has been established.

Follow-up studies have been carried out to monitor children exposed to variable alcohol consumption during pregnancy: the children underwent a psychomotor development or IQ (intellectual quotient) test as babies or young children. Some of these studies have shown that children exposed to more moderate levels of alcohol during pregnancy than children affected by FAS have intellectual deficits or behavioural disorders similar, albeit less marked, to those presenting with FAS. A reduction in IQ of the order of 5 to 7 points in children of pre-school or school age has been detected in cases where maternal alcohol consumption was more than or equal to 2 to 3 glasses/day. One of the studies that monitored children up until 14 years of age, demonstrated the effects of such consumption during pregnancy on memory and arithmetic skills and on the children's reading ability. A threshold effect on cognitive functions corresponding to the consumption of 2 to 3 glasses/day cannot, however, be

deduced. For lower rates of consumption, only studies involving a very large number of subjects could establish the presence or absence of any effects. Excessive one-time consumption (at least 5 glasses at one time) during pregnancy has also been linked with intellectual deficits in children. Epidemiological studies thus confirm the harmful effects on birth weight and on cognitive functions in children of the consumption of 2 glasses/day, some studies having demonstrated a dose-effect relationship. It should be remembered that, from the results obtained in experimental studies, it is not possible to confirm a dosing threshold under which maternal alcohol consumption during pregnancy has no risk to the offspring.

The hypothesis regarding the protective role of moderate alcohol consumption on cognitive functions in the elderly has yet to be demonstrated.

In the elderly, dementia, characterised by deterioration in cognitive functions associated with a loss of autonomy, is a common condition affecting 5% of over 65 year-old subjects. Two forms of dementia have been described – vascular dementia or degenerative dementia (Alzheimer's disease in almost 70% of cases).

In the initial case-control studies of Alzheimer's disease, alcohol consumption was investigated to the same extent as many other potential risk factors such as smoking, family history, education, cranial trauma or exposure to aluminium. A meta-analysis comprising 11 of these studies did not reveal any effect of alcohol consumption on the risk of dementia or Alzheimer's disease, regardless of the level of consumption considered (absence, light, moderate, high). However, the collection bias is important in these case-control studies where information relating to individual alcohol consumption can be obtained only from an informant.

Only two follow-up studies have focused on incidental cases of dementia and Alzheimer's disease. The initial (American) study found no significant correlation with consumption levels but the limited number of subjects (513) restricted the power of this study. The second (French) investigation including 2 273 subjects of both sexes, monitored for a period of 3 years, indicates a significantly reduced risk of dementia (relative risk = 0.19 with a 95% confidence interval of 0.05-0.66) in the group consuming 3 to 4 glasses/day, the reference group being non-consumers (abstinent or less than one glass per week). Similar results can be found if only the cases of Alzheimer's disease are taken into account. No other study on incidental cases of dementia has so far been published. The risk of a publication bias (non-publication of negative results, for instance) cannot be overlooked.

Even if cognitive deterioration is not necessarily followed by a progression towards dementia, examination of the relationship between alcohol consumption and cognitive function is justified. The results of cross-analyses globally corroborate the fact that moderate alcohol intake confers a protective effect, which is not, however, always found. Two follow-up studies including the French EVA (*Epidemiology of vascular ageing*) study, have highlighted a link between alcohol intake exceeding 2 glasses/day and good cognitive performance, but this association is evident only in women. The lack of correlation in men cannot be readily explained even if the role of individual and environmental (metabolism, hormonal status, lifestyle…) factors could be advanced. In those over 60 year-old, the literature tends to suggest, but not to confirm, the hypothesis that moderate alcohol consumption has a protective effect on cognitive functions. It is, however, premature to attach much weight to this hypothesis since large-cohort current studies have yet to be published.

Moderate alcohol consumption is associated with a reduced cardiovascular risk in epidemiological studies

Various studies have evaluated the effects of alcohol consumption on the risk of onset of coronary disease. Moderate consumption is associated with a reduction of the order of 10 % to 50 % in terms of the risk of onset of ischaemic heart disease. The data obtained in ten prospective studies confirm that the risk decreases up to the consumption of approximately 20 g/day in men and up to 10 to 20 g/day in women. As regards higher levels of consumption, the analysis cannot establish a favourable correlation between alcohol consumption and cardiovascular risk. Finally, all published data show that this protective effect is not associated with a particular type of beverage. Furthermore, dietary habits could intervene in this protective effect.

Alcohol consumption is associated with a reduced risk of ischaemic cerebrovascular accident (CVA) and with an increase in the risk of haemorrhagic CVA. This effect is not associated with a specific type of beverage either. Overall, the increased risk of haemorrhagic CVA is greater than the reduced the risk of ischaemic CVA, which leads to a dose-dependent increase in the overall risk of CVA in consumers. This risk is especially higher after acute, excessive alcohol consumption.

There are very few prospective studies available focusing on the effect of alcohol consumption on the risk of onset of arteriopathy in the lower limbs. Moderate alcohol consumption (up to 24 g/day) would be associated with a reduced risk, but these results must be confirmed. Alcohol-induced myocardiopathy is due to a combination of heart failure and a high alcohol intake, and gradually regresses on withdrawal. Alcohol consumption is also linked with a more frequent onset of cardiac, chiefly atrial, arrhythmias, the mechanisms of which have yet to be elucidated. These effects are mainly observed in the event of excessive consumption and regress on withdrawal. However, the risk of sudden death is increased by 73% in subjects consuming more than six glasses/day, when compared with abstainers.

The effect of alcohol consumption on various cardiovascular risk factors has been widely explored. A dose-dependent increase in high-density lipoprotein (HDL) levels– a protective factor against a coronary disease – has been observed whilst low-density lipoprotein (LDL) levels – a factor promoting the development of atherosclerosis, is barely modified if at all. This effect has also been observed for the HDL apolipoproteins. The effect of alcohol on lipid parameters would be mediated by the inhibition of a HDL catabolism enzyme – hepatic triglyceride lipase, and by an effect on the cholesterol ester transfer protein. Moreover, the pattern of alcohol consumption would also influence the lipid profile. Moderate, regular consumption would increase the HDL level whilst irregular, excessive consumption would be associated with an unfavourable lipid profile. On the other hand, the type of beverage does not appear to have any substantial effect on the lipid profile.

Alcohol consumption is associated with a reduction in several haemostasis factors involved in coagulation, namely platelet aggregation, fibrinogen levels, antithrombin III levels, von Willebrand factor and factor VII (the negative relationship between factor VII and alcohol consumption has not, however, always been found). Alcohol consumption also induces an increase in the concentration of the plasminogen tissue activator, thus enhancing the anti-thrombotic properties of alcohol.

Regular alcohol consumption is associated with a gradual increase in systolic and diastolic blood pressure in both sexes, especially at levels exceeding 20 g/d (approximately 2 glasses). This effect on blood pressure has been observed in most of the countries studied, including France. The frequency of hypertension thus increases by 50% in men following consumption

of between 36 and 60 g/day, and doubles for higher levels of consumption. In women, the prevalence of hypertension doubles in the case of alcohol intake of the order of 36 g/day. This hypertensive effect would be independent of the type of beverage consumed. Contrary to the idea postulated by certain authors, alcohol consumption of the order of 1 glass/day does not appear to have a marked, beneficial effect on blood-pressure values. At most, it can be said that the risk of hypertension associated with an alcohol intake of less than 20 g/day has not been clearly demonstrated.

Alcohol consumption is associated with an established or probable increase in certain forms of cancer

The correlation between alcohol and cancer has been confirmed in the scientific literature for many years. The link between alcohol consumption and cancers of the upper respiratory/digestive tracts (mouth, pharynx, larynx and oesophagus) and of the liver is considered established. Similarly, the link with breast cancer and colorectal cancer is deemed to be probable. Lastly, a relationship with lung cancer is considered possible. Alcohol consumption certainly does not affect bladder cancer; it is unlikely to affect cancer of the stomach or pancreas and probably does not affect prostate or kidney cancer. Only those cancer sites for which the link with alcohol consumption is considered to be established or probable are considered here.

The relationship between alcohol consumption and the risk of cancer of the mouth and pharynx is consistently reported in the literature. It has been investigated in about twenty case-control studies and ten cohort studies. In virtually all of the studies, the risk is multiplied 2- to 5-fold. Some of the studies report an individual estimation of alcohol consumption and characteristics (smoking, diet, for instance) likely to affect it or be influenced by it, and on the basis of which, adjustments have been made. The combined effect of alcohol consumption and smoking has been investigated. Compared with non-drinkers and non-smokers, alcohol consumption exceeding 45 g/day in non-smokers doubles the risk of cancer of the oral cavity and pharynx whereas a high rate of smoking (> 40 cigarettes/day) and of alcohol consumption (> 45 g/d) multiplies the risk by 15.

All epidemiological studies carried out since the 1950s have found an increased risk of cancer of the larynx in conjunction with alcohol consumption. Several studies have demonstrated a dose-effect relationship. According to the studies, the level of risk involved varies from 1.4 to 5.4 in subjects with a high consumption compared with those with a low consumption. In these studies, the risk of laryngeal cancer does not depend on the type of beverage consumed. A large-scale, multicentre study carried out in Italy, Spain and France analysed the effect of alcohol intake on the risk of cancer of the larynx, according to the anatomical site. A significant increase in the risk was observed with the quantity of alcohol after adjustment for smoking, age and geographical country of residence. This combination is more marked for cancers affecting the supraglottal region (junction between ingested and inhaled substances, which is thus exposed both to liquid alcohol and to alcohol vapours) than for those affecting the lower region (exposed only to the volatile part of alcohol). The combined effect of alcohol consumption and smoking also seems to vary depending on the anatomical location of the cancer. This European multicentre study demonstrated an alcohol effect regardless of the smoking effect in both the endolaryngeal region (risk of cancer associated with the daily consumption of more than 120 g of alcohol reaching 2.7 after elimination of the smoking effect by statistical adjustment) and the hypo- and epipharynx (risk reaching 10.2).

As to oesophageal cancer, uniform results were recorded in epidemiological studies. The risk of cancer of the oesophagus associated with the consumption of alcoholic beverages increased 2- to 6-fold in most studies. Smoking was not systematically taken into account. Most studies were carried out in regions of standard alcohol consumption. In France, the dose-effect relationship and the interaction with smoking were studied in Ille-et-Vilaine and Calvados. These studies focused on a large number of incidental cases compared with controls typical of the two regional populations, at a time when alcohol consumption in France was the highest in the world. The amount consumed seems to be more important than the type of alcohol. Alcohol and smoking have a cumulative effect on the risk of oesophageal cancer. Compared with moderate smokers and drinkers (fewer than 9 cigarettes/day and less than 39 g of ethanol/day), high alcohol consumption increases the risk to a substantially greater extent (RR = 37) than a high rate of smoking (RR = 5). The risk for subjects who drink and smoke a lot (> 20 cigarettes/day and > 80 g of ethanol/day) is extremely high (RR = 44).

In consumers of excessive quantities of alcohol, hepatocellular carcinoma occurs only in patients who have already developed alcohol-induced cirrhosis. When cirrhosis is present, the likelihood of developing hepatocellular carcinoma at 5 years has been estimated at 15-20 %. In male patients with alcoholic cirrhosis, alphafoetoprotein serum levels exceeding 15 ng/ml and the presence of serological markers of infection due to the hepatitis B or C virus are variables that are associated with a high risk of hepatocellular carcinoma.

About forty case-control studies and more than ten cohort studies have documented the risk of breast cancer associated with excessive alcohol consumption. Furthermore, three meta-analyses have been carried out to assess this relationship. Despite some variability in their results, all these studies indicate an increase in the risk of breast cancer with alcohol consumption. The risk levels reached are, however, moderate, with an increase of the order of 10% per dose of 10 g ethanol consumed. The type of alcohol consumed does not appear to be an important factor for consideration. Additional biological, epidemiological and experimental studies are necessary to explain the mechanisms underlying this relationship and to investigate any interactions, particularly with hormone status and diet. In fact, some studies appear to demonstrate a variable effect of alcohol depending on whether it is administered concomitantly with hormone replacement therapy, the combination of the two accentuating the risk, and depending on the hormone-dependent nature of the tumour. Furthermore, adequate folate consumption could reduce the excess risk of alcohol-related breast cancer in some patients.

Several case-control and cohort studies have been published on the correlation between alcohol consumption and colorectal cancer or adenomatous polyps (considered to be pre-cancerous lesion). The results are, on the whole, consistent, regardless of whether or not the authors analysed the results per gender or cancer site (colon or rectum). The risk level associated with the consumption of over 30 g of ethanol per day varies from 1.5 to 2 in the cohort studies but, in some of them, alcohol consumption reduces the risk. Certain studies have noted an increased risk associated with beer consumption. Consideration of adjustment factors is important. In the particular case of colorectal cancer, mainly nutritional factors are involved, dietary habits varying considerably with alcohol consumption.

The effect of ethanol as a solvent for carcinogenic substances, the induction of microsomal enzymes (P450 cytochromes), the weakness of the immune system and free radical production are some of the mechanisms involved in the development of cancers. Intervention of free radicals was demonstrated in a study during which the chronic administration of ethanol following that of N-nitrosomethylbenzylamine – a potent carcinogenic agent – increased the incidence of oesophageal tumours. Moreover, the

administration of ethanol at concentrations of 5 % to 25 % increased the penetration of tobacco-specific carcinogens into the oral mucosa. In addition, ethanol increases the proliferation and reduces the differentiation of neoplastic, intramucosal cells of head and neck carcinomas. CYP2E1 could also activate a certain number of pro-carcinogens to form carcinogens (nitrosamines, etc.).

As regards the risk of breast cancer, apart from its effects on the initiation and promotion of carcinogenicity associated with the chemical inducers of breast tumours, ethanol increases the migration and invasion of cancerous cells into the breast. Alcohol therefore appears not only to be a carcinogenic risk factor, but also promotes the invasion of breast cancer and metastases. The mechanism generally involved is the ethanol-mediated change in liver metabolism, which increases the level of circulating hormones.

The development of alcohol-related diseases is partly subjected to individual genetic susceptibility

Individual susceptibility to the effects of alcohol may be due to the existence of metabolic enzyme polymorphism. In the polygenic alcohol dehydrogenase group, the *ADH2* and *ADH3* genes are polymorphic. The *ADH2*1, ADH2*2* and *ADH2*3* alleles code for β1, β2 and β3 sub-units of the dimeric enzyme, respectively. Although they differ by just one single amino acid, these isoenzymes have quite distinct catalytic properties. The *ADH3*1* and *ADH3*2* alleles code for the γ1 and γ2 sub-units, respectively, which differ in terms of activity. The frequency of these different alleles varies with the ethnic group. In Caucasoids and Afro-Americans, alleles *ADH2*1* are mainly found. These code for an enzyme having a strong affinity for alcohol, but a weak enzymatic activity. In Asians, the most frequent alleles are *ADH2*2,* which express an enzyme with strong activity but weak affinity. These subjects seem to have a reduced risk of excessive alcohol consumption. Although polymorphisms *ADH2*2* and *ADH3*1* are linked, allele *ADH3*1* has not appeared to affect the level of alcohol consumption. Subjects with alleles *ADH2*3* (15 % of Afro-Americans) should metabolise alcohol much faster than others, but the increase observed was only 20 %. Factors such as the rapidity of NAD^+ regeneration (the coenzyme of ADH and ALDH) or the accumulation of acetaldehyde actually represent the limiting factors of the enzymatic reaction.

Frequency (%) of ADH alleles according to ethnic group (according to Bosron and Li, 1987)

	ADH 2-1	*ADH 2-2*	*ADH 2-3*	*ADH 3-1*	*ADH 3-2*
Caucasoids	> 85	< 15	0	60	40
Asians	15	85	0	95	5
Afro-Americans	85	0	15	85	15

Genetic polymorphism was detected in the ALDH2 gene. The *ALDH2*1* allele codes for a highly active enzyme, present in all Caucasoids, whilst *ALDH2*2* codes for an inactive enzyme found in 50% of Asians. This inactive ALDH results in an accumulation of acetaldehyde related with facial flushing and signs of intolerance to alcohol ("Antabuse effect"). The presence of the *ALDH2*2* allele protects, via a dissuasive effect, against excessive alcohol consumption. The consequences of excessive alcohol consumption are, however, more damaging in individuals who drink despite this genetic deficiency.

Several genetic polymorphisms have been described for *CYP2E1*. The *Rsa I* (5'-flanking region of the gene) restriction site can characterise alleles c1 (common) and c2 (muted). This mutation increases the gene transcription level *in vitro* but contradictory results concerning the expression or activity of the enzyme have been obtained *in vivo.* The *Dra I* site (intron 6), which is partly linked to the *RsaI* site, can characterise alleles D and C. The incidence of muted alleles of the CYP2E1 gene is relatively low in Caucasoids (2 % to 8 %) compared with

Asians (23 % to 28 %).

The genetic polymorphism of ethanol metabolism enzymes can therefore impact upon diseases associated with excessive alcohol consumption. The presence of allele *ADH2*2* (chiefly in Asian populations) seems to be associated with an increased risk of cirrhosis. Alleles *ALDH2*1* and *ADH2*1* are more frequently found in patients with alcoholic cirrhosis compared with non-consuming controls. Recent studies do not indicate a significant correlation between the *RsaI* polymorphism of CYP2E1 and alcohol-related liver diseases. Lastly, polymorphisms concerning various pro- or anti-inflammatory cytokines (TNFα, IL10, IL1 receptor antagonist) could be associated with certain types of alcohol-induced liver diseases.

Many studies have been devoted to research on interactions between genetic polymorphism and the onset of alcohol-related cancers. The presence (chiefly in Asian populations) of allele *ALDH2*2* is linked with an increased risk of all cancers, and particularly those of the upper respiratory/digestive tracts.

The effects of genotype *ALDH2*1/2*2* on the risk of cancer in Japanese consumers of excess alcohol

Type of cancer	*Odds ratios* (confidence intervals)
All	5.4 (3.5-8.4)
Oral cavity	18.5 (7.7-44.4)
Oesophagus	13.5 (8.1-22.6)
Multiple	21.0 (6.9-64.5)
Multiple oesophageal	54.2 (11.5-255.2)

In Asian populations, *ADH2*1* also increases the risk of cancer of the upper respiratory/digestive tracts, especially in conjunction with *ALDH2*2*. This polymorphism, which causes a slower alcohol metabolism, could thus "relieve" the short-term adverse effects of ALDH2*2 (Antabuse effect) and promote alcohol consumption. The risk of oropharyngeal cancer could be higher in subjects combining excessive alcohol consumption with a rare CYP2E1 allele. Furthermore, associations have inconsistently or marginally been described between certain genetic variants of the enzymes of the metabolism of xenobiotics (glutathione *S*-transferases - GST, *N*-acetyl transferase 2) and cancers of the upper respiratory/digestive tracts in Asian populations, but not in Europe. In the case of breast cancer, interactions between alcohol consumption and polymorphisms have been observed in Asians (null alleles *GSTM1* and *GSTT1*) and in Caucasoids (*ADH3*1-1*). Prior to menopause, the risk associated with these functional genotypes is higher in women consuming a greater amount of alcohol.

Diseases associated with excessive alcohol consumption and influenced by genetic polymorphism

Genetic polymorphisms		Diseases
Higher risk	Lower risk	Cirrhosis
*ADH2*2*		Other alcohol-induced liver diseases
TNFα, IL10, IL1 receptor		Cancer of the upper respiratory/digestive tracts
*ALDH2*2*, *ADH2*1*[1], CYP2E1, GST[1], NAT[1]		Breast cancer
GSTT and GSTM zero[1], *ADH3*1-1*[2]		Coronary disease
	CETP *Taq1 B2B2*, *ADH3*2-2*	

[1]: in Asian populations; [2]: in Caucasioid populations

Finally, recent studies have examined the diminished risk of coronary disease associated with moderate alcohol consumption depending on *ADH3* polymorphism. A moderate alcohol consumption is associated with a reduced risk of infarction, regardless of the ADH3 genotype, but the association is most noticeable in *ADH3*2-2* homozygous men drinking at least one glass of alcohol per day. These men have higher HDL-cholesterol levels. This result is consistent with the hypothesis that a slower elimination of alcohol accentuates the beneficial cardiovascular effect. Moreover, alcohol-mediated protection against

cardiovascular risk is also associated with the *Taq 1 B2B2* genotype of CETP (*cholesteryl ester transfer protein*), through increased HDL-cholesterol levels. In both instances, this protective effect is due to interaction with ethanol.

The effects of alcohol consumption interact with the nutritional status

Nutritional status is influenced by alcohol consumption. This may be a direct effect whereby food intake is replaced by alcohol consumption, or an indirect effect via disease-related malabsorption. When alcohol consumption remains moderate, the alcohol calories are added to the total energy intake. However, when consumption increases, alcohol partly replaces the glucidic intake followed by a decrease in protein, lipid and vitamin A, B and C (especially thiamine) with levels potentially falling below the recommended intake. Calcium, iron and fibres are also depleted. Nevertheless, the nutritional status of subjects who consume alcohol can vary considerably, thus reflecting to a large extent the differences in their diet. Patients who consume alcohol to excess can, therefore, have a normal caloric intake.

Nutritional deficiencies potentiate the effects of alcohol and alcohol consumption affects nutrient metabolism. Protein malnutrition reduces lipoprotein secretion, which potentiates the storage of lipids in the liver under the direct influence of alcohol. In cases of similar alcohol consumption, undernourished patients will present with a higher and more extended blood alcohol peak, wider over time, than properly nourished individuals. Muscle fibre atrophy, evident on biopsy, may appear in the most undernourished of chronic, hospitalised alcoholic patients.

Undernourished alcoholic patients absorb folic acid less readily than better nourished controls, although the reasons for this difference are not very clear. Alcohol also potentiates the consequences of folate deficiency by accelerating the onset of megaloblastic anaemia and by reducing the response to folic acid treatment in deficient subjects. Malnutrition also contributes to vitamin A liver deficiency in cases of alcohol-induced liver disease. This deficiency can, however, also occur in patients who are apparently better nourished. Alcohol potentiates the effects of vitamin A deficiency on carcinogenicity. Paradoxically, hypervitaminosis A can also be toxic (cancer, foetal deformities and hepatotoxicity) and could be exacerbated by alcohol, as seen in laboratory animal studies. In the general population, alcohol consumption is positively associated with weight in men but to a lesser significant extent than anticipated, given the energy content of this molecule (7 kCal/g). In women, alcohol consumption is associated with weight loss. Several reasons would, however, justify weight gain: the energy provided by alcohol is combined with that obtained from other nutrients, at least up to a certain consumption level. Alcohol intake (e.g. an aperitif) before a meal, stimulates food intake. Energy loss due to alcohol-induced thermogenesis is only 15 %. Finally, alcohol inhibits the oxidation of lipids, which become more readily stored in the adipose tissue. On the other hand, the alcohol-mediated increase in insulin susceptibility would deplete the quantity of fatty acids stored by the adipose tissue by reducing blood insulin levels. An American study has thus highlighted a 40% decrease in the risk of insulin-dependent diabetes in women consuming two glasses of alcohol per day following adjustment on the body mass index. Alcohol consumption accompanied by a sedentary lifestyle and a diet rich in lipids promotes abdominal obesity. The method of consumption, however, appears to affect obesity. With an overall similar consumption, regular (daily) consumers are thinner than those who do not consume alcohol on a daily basis.

In intervention studies, overweight subjects use alcohol-related calories more efficiently. They increase their weight whereas slim subjects tend to lose weight. These results are

consistent with the hypothesis of susceptibility to insulin. In fact, in insulin resistant, obese subjects, the sensitising effect of alcohol could be inhibited or negligible. Similarly, in these overweight subjects, the lack of any beneficial effect of alcohol on HDL – cholesterol (HDL-C) levels may be associated with their insulin resistance.

The effect of alcohol on global and cardiovascular mortality varies according to consumption levels

It is well known that excessive alcohol consumption may be responsible for death by intoxication, accidents or violence and that long-term usage increases the incidence of cirrhosis and of certain types of cancer (tongue, oesophagus, pharynx, liver and probably breast cancer in women). More recently, the hypothesis according to which low or moderate consumption could reduce the risk of ischaemic heart disease has been corroborated in several prospective studies.

According to the English physicians' cohort (over 10 000 subjects born between 1900 and 1930), the deaths reported between 1978 and1993 were compared against the declarations of alcohol consumption made in 1978. Amongst these elderly or rather elderly subjects, a consumption of 10 to 20 g/day was associated with a lower mortality rate (taking all causes into account) than in the case of non-consumers or a higher consumption level. Beyond an alcohol intake of 30 g/day, consumption was associated with an increased mortality rate.

In an American cohort (490 000 men and women with an average age of 56 years), the 46 000 deaths occurring during the 9-year follow-up period were compared with the declarations regarding smoking and alcohol consumption made in 1982. After adjustment for other risk factors, the breast cancer mortality rate was 30 % higher in women reporting a consumption of at least one glass per day compared with non-consumers. The mortality rates for cardiovascular causes were 30 % to 40 % lower amongst men and women reporting a consumption exceeding 10 g/day than in non-consumers. However, the correlation with the consumption level is low. Global mortality rates were lowest in men and women declaring daily consumption of 10 g. Taking all causes of death into account, the mortality rate increases with a higher consumption, particularly in subjects under 60 years of age with a lower risk of cardiovascular disease. Alcohol consumption is associated with a lower mortality rate (taking all causes into account) between the ages of 35 and 69, whereas smoking doubles this risk.

In France, a prospective cohort (over 30 000 men between 40 and 60 years of age) from the Eastern region was monitored for 12 to 18 years. Moderate wine or beer consumption was associated with a lower risk of cardiovascular disease. Taking all causes of death into account, only the daily consumption of 22-32 g of alcohol in the form of wine was associated with a lower mortality rate.

Most studies have been carried out on men and apparent beneficial effects were observed only in subjects over 40 years of age. Thus, there is little or no evidence of a lower cardiovascular mortality rate associated with low or moderate alcohol consumption in subjects under 40 years old. However, given the low incidence of cardiovascular diseases in young people, it seems difficult to detect a protective effect of alcohol in this population except in studies conducted with a very large patient cohort. In the few studies carried out in women, a beneficial effect (40% reduction in coronary disease) was observed with a consumption of less than de 20 g/day (10-90 g per week). This is particularly the case after 50 years of age.

In these studies, many factors influence the results. For instance, the reference group of non-

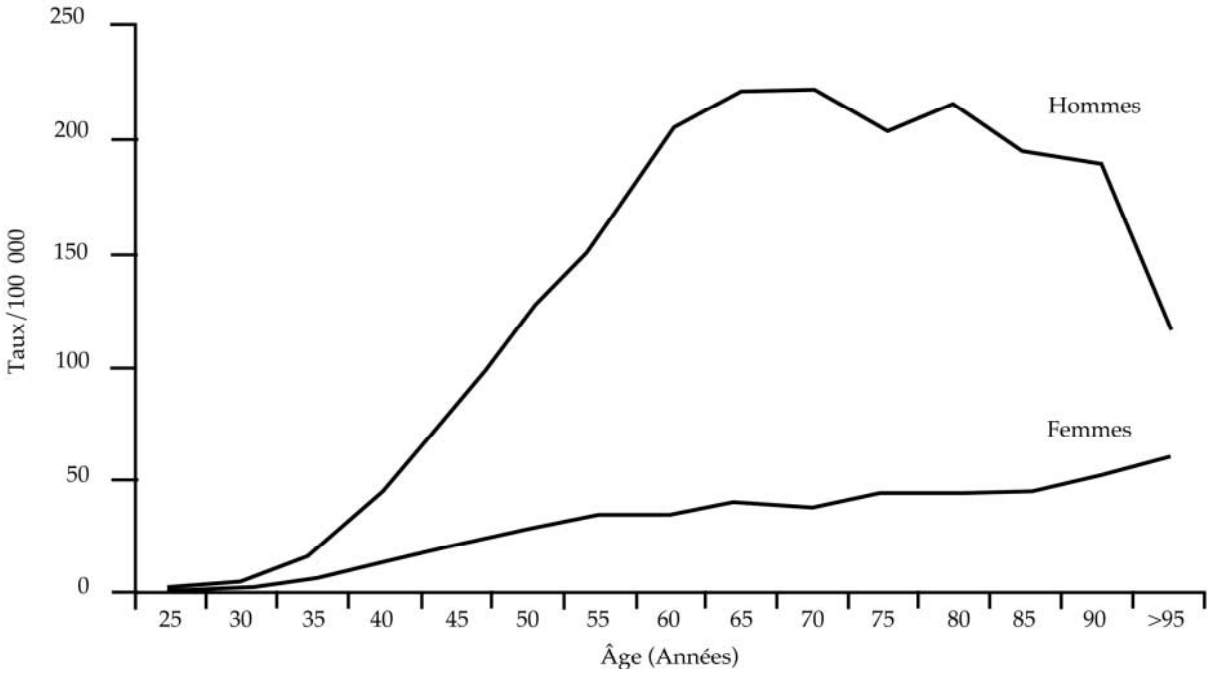
consumers may include former consumers or subjects at high risk of cardiovascular disease. The change in consumption habits may also affect the results. Alcohol consumption generally tends to decrease with age. The variation over time may boost the correlation between light consumers and the reduction in cardiovascular events. Furthermore, the existence of other confounding factors cannot be overlooked. The effects of alcohol on the cardiovascular system might not be due to a direct effect but rather to social class, smoking status, physical activity or type of personality. Recent studies have attempted to adjust these factors or to take them into account by stratifying the groups. The adjustment does not appear to modify the benefit observed.

The fact that one type of beverage (wine, beer or spirits) could have a greater cardiovascular "protective" effect than the other two types of alcohol has always been subject to debate. All of the case-control and prospective studies carried out in various parts of the world do not indicate that one type of drink possesses more cardio-protective properties than the other two. The authors conclude that the lower mortality risk and thus the beneficial effect on cardiovascular morbidity could be attributed to ethanol itself.

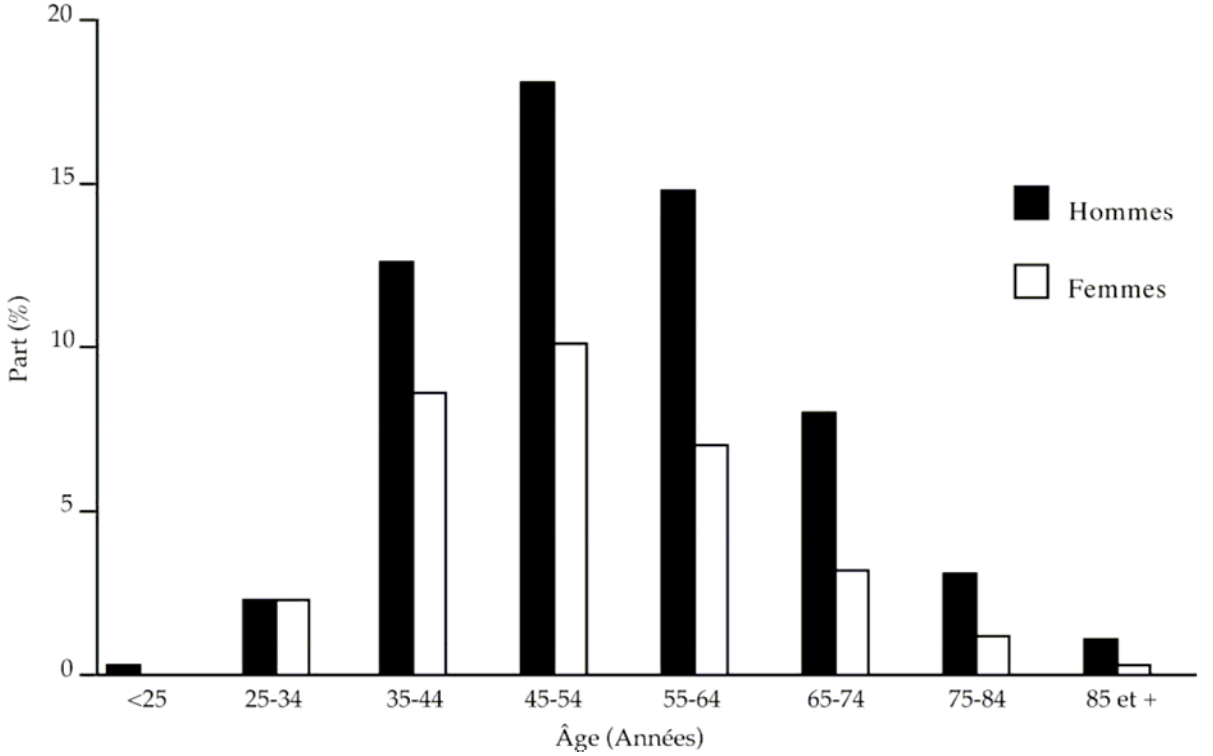
Geographical (or ecological) studies comparing the mortality rate of a given country with the average consumption of various alcoholic beverages per inhabitant (*per capita*), tend to find a greater reduction in terms of cardiovascular risk associated with wine consumption (compared with beer and spirits). The results of three prospective studies on this topic, including one in France, corroborate this observation but the authors recognise the fact that most individuals consume several types of drinks. The majority of prospective studies carried out show that wine, beer and spirits have an equally protective effect, the differences occasionally observed between the various types of alcoholic beverages probably being due to differences in cohort characteristics. Some of the protective effects reported in wine consumers could thus be associated with lifestyle or diet.

The overall mortality rate associated with chronic alcohol consumption is higher in France for populations over 35 years old

Apart from violent deaths (accidents, suicides…), alcohol accounted for 4.3% of all deaths recorded in France in 1998, i.e. a total of 23 000 deaths: 51% were due to cancers of the upper respiratory/digestive tracts, 38% to cirrhosis and 11% to "alcohol dependency" (term taken from the nomenclature used to compile death certificates). The number of deaths directly due to alcohol was the same as that reported for lung cancer, and lower than the number of deaths due to ischaemic heart disease (45 000) or cerebrovascular disease (42 000). The mortality rate is five times higher in men than in women. Nevertheless, the cirrhosis-related mortality rate is proportionally higher in women, thus confirming female susceptibility to this disease.



Mortality rate* associated with chronic alcohol intoxication according to gender and age (France, 1998) * number of deaths per 100 000; reference population: 1990 figures, both sexes



Percentage of deaths due to chronic alcohol intoxication (excluding violent deaths) according to age and gender (France, 1998)

The number of deaths due to chronic alcohol intoxication varies according to age in men and women, but reaches a peak in the 45-54 year-old group. Deaths due to alcoholisation fell by 44% in men and 40% in women between 1980 and 1998. Whereas the mortality rate (taking all causes of death into account) in the working age population is three times greater in workers and employees than in senior executives and professionals, the mortality rate due to alcoholisation is ten times greater in the first category.

Recommendations

A synthesis based on a critical analysis of the literature has identified the effects of alcohol exposure on various organs, its role in the development of various diseases (cardiovascular diseases, cancers, cirrhosis of the liver, foetal deformities, etc.) and the better understanding of their mechanisms .

Although recent epidemiological studies have revealed an association between alcohol consumption and a reduced risk of coronary disease – a frequent cause of death in developed countries – it remains to be seen whether this correlation is due solely to alcohol consumption or whether additional factors such as lifestyle are involved, and to understand the biological mechanisms of such an effect.

Some studies have thus shown that even a moderate consumption of alcohol is a factor of disease and excessive mortality whereas others have shown that alcohol can protect the coronary system. The notion of "moderate alcohol consumption", however, fluctuates according to authors. It is therefore essential to refer to consumption in terms of grams of alcohol per unit of time in order to compare the various studies.

Precise dosing thresholds for the effects of alcohol cannot be established from the studies analysed, probably because there is a continuum in the onset of the various diseases depending on consumption level. Moreover, the investigation of these thresholds is made difficult by the absence of a reliable tool for measuring real alcohol consumption. The development of such a tool would allow real advances to be made in understanding the relationship between alcohol and health (threshold effect, dose-effect relationship).

Minimal (or optimal) consumption cannot be recommended for the general population. In fact, risk consumption differs in men and women and depends on weight, age and concomitant risk factors. There are individual differences in effects relating to consumption patterns, diet and genetic predisposition. These various situations must be considered and the messages adapted accordingly in information and prevention campaigns.

Information and prevention

INTRODUCE INFORMATION AND PREVENTION CAMPAIGNS TAKING INTO ACCOUNT THE DIFFERENCES IN ALCOHOL TOXICITY IN MEN AND WOMEN

Mortality associated with chronic alcohol consumption is five times higher in men than in women. In 1998, the mortality rate at 65 years of age was 220 per 100 000 in men and 40 per 100 000 in women. Between 45 and 54 years, the number of alcohol-related deaths accounted for 18% and 10% of the global mortality rate in the same year for men and women respectively.

Women are at risk of developing cirrhosis following a lower consumption level than men. The risk of developing an alcohol-related liver disease in an otherwise healthy individual becomes significant (relative risk multiplied by 3) when a consumption level of 50 g per day in men and 30 g in women is reached. The duration of exposure, which must also be taken into account, seems shorter in women.

Women are probably at risk of developing breast cancer with relatively low alcohol

consumption. As from 10 g/day, a meta-analysis revealed an increased risk of 10 % for a 10-g/day increase in consumption.

In women, the protection against cardiovascular disease due to alcohol consumption is apparent with consumption of lower quantities of alcohol than by men. According to all of these studies, the cardiovascular mortality risk falls by 40 % to 50 % following consumption of 10-40 g/day in men and 2-20 g/day in women.

In women, the thresholds are lower for risks and protective effects. This is probably due to a higher blood alcohol level for the same quantity of alcohol consumed. The alcohol ingested by women is distributed in a smaller volume of free water than in man (0.50 l/kg and 0.65 l/kg respectively), and the first-pass metabolism seems diminished in women. Moreover, the effects of alcohol could differ depending on a woman's hormone status (menopause, hormone replacement therapy). Experiments have shown that female hormone levels are sensitive to the hepatotoxicity of alcohol and are also involved in breast cancer.

INTRODUCTION OF INFORMATION AND PREVENTION CAMPAIGNS ACCORDING TO VARIOUS AGE GROUPS

For the 18-44 year age group

Between the ages of 18 and 44 years, excessive alcohol consumption is responsible for death by intoxication, accidents (truck drivers in particular) or acts of violence. Before the age of 35, mortality due to chronic intoxication accounts for just 1 % of the general mortality rate in France.

The potential beneficial or harmful effect of alcohol consumption on cardiovascular disease in this age group cannot be derived from the data currently available.

Most alcohol-related diseases, and cirrhoses in particular, are due to the consumption of alcohol over a period of several years. Based on indirect arguments, cirrhosis is estimated to develop over a period of 20-25 years. Excessive consumption between the ages of 18 and 40 may well cause the subsequent development of this type of condition.

Regarding cancer, there are no data to specify the minimal exposure period, the effect of alcohol consumption at different ages (especially for breast cancer) and the impact of stopping alcohol consumption on risk reduction.

For the 45 to 64 year age group

Between the ages of 45 and 64 years, the mortality rate due to chronic alcohol intoxication accounts for 20% to 25% of male deaths in France.

Beyond 40 years of age, alcohol consumption affects the development of a certain number of diseases, especially cardiovascular and liver diseases and cancers. This effect depends on the dose consumed and the duration of exposure (excessive consumption can take place before the age of 40).

As regards cirrhoses, the average age of patients at the time of diagnosis is 50 to 60 years. The most severe alcohol-related liver diseases (acute major alcoholic hepatitis, alcoholic cirrhosis) can be life-threatening with a survival rate of 5 years ranging from 20% to 60%. Even if cirrhosis does not regress once alcohol consumption has been stopped, this is associated with a 30% increase in life expectancy at 5 years.

The correlation between alcohol consumption and various types of cancer has been

established for cancers affecting the upper respiratory/digestive tracts (mouth, pharynx, larynx and oesophagus) and the liver. Alcohol consumption probably increases the risk of breast cancer (as from consumption of 10 g/day in women) and colorectal cancer.

Moderate alcohol consumption (20 g/day for men and 10 g/day for women) is associated with a reduction of the order of 10 % to 50% in the risk of onset of ischaemic heart disease. The data are contradictory beyond daily consumption of 10 to 20 g. Furthermore, the risk of haemorrhagic cerebrovascular accident increases with alcohol consumption and especially after continued excessive consumption.

Beyond the 65 year age group

In France, the mortality rate due to chronic alcohol consumption reaches a peak between the ages of 55 and 74 years in men, even though it represents a mere 4% of the global mortality rate. The mortality rate for cirrhosis reaches a peak in this particular age group.

In over 60 year-old subjects, the results of two French studies suggests that alcohol has a protective effect on cognitive functions at moderate doses. The first study reports a significantly lower risk of dementia or Alzheimer's disease in the group consuming 3 to 4 glasses of alcohol per day when compared with the non-consumers (abstinent or less than one glass per week). The second study highlights the correlation between alcohol consumption exceeding 2 glasses/day and good cognitive performance only in women.

Changes in the lean/fat mass ratio during the ageing process modify the distribution volume of alcohol and could affect the outcome of alcohol consumption (e.g. a lower threshold for risks and protective effects).

Moreover, free radical production, which increases with age (radical theory of ageing), is increased by alcohol consumption.

TO TAKE CONSUMPTION LEVELS INTO ACCOUNT IN INFORMATION AND PREVENTION CAMPAIGNS

From 0 to 20 g/day

Most of the studies have not evinced an increased risk of morbidity in this consumption range. However, a meta-analysis suggests a moderate increase of 10% per 10-g dose in the risk of breast cancer in women, already from a daily consumption of 10 g. The effect of alcohol on the risk of breast cancer, however, is modulated by a certain number of factors and the female hormone status in particular.

A reduction in the cardiovascular mortality rate is apparent in both men and women in the case of real consumption of less than 20 g/day.

From 20 to 50 g/day

The risk of cirrhosis is increased in this consumption range as from 30 g/day on average in women and 50 g/day in men.

There is a moderate increase in hypertension and in the risk of haemorrhagic cerebrovascular accident in both men and women. Although the risk of mortality for all cardiovascular causes of death appears to be reduced in men and women, the overall mortality rate could already increase from 20 g/day and 30 g/day in women and men, respectively.

Some case-control studies suggest a moderate increase in the risk of cancer of the upper

respiratory/digestive tracts and of cancer of the colon and rectum in both men and women. In the case of colorectal cancer, alcohol is probably combined with other dietary risk factors.

Beyond 50 g/day

The risk of cirrhosis has been clearly demonstrated. This is accompanied by a certain increase in liver cancers, which would tend to affect approximately 20 % of subjects with cirrhosis.

The risk of developing cancer of the upper respiratory/digestive tracts is at least doubled compared with non-consumers of alcohol, and can be multiplied by 10 or even 40 when alcohol consumption is combined with chronic smoking (relative risk of 37 for oesophageal cancer).

TO TAKE SPECIFIC SITUATIONS INTO ACCOUNT IN INFORMATION AND PREVENTION CAMPAIGNS

Pregnant women

The most serious effect of prenatal alcohol exposure – foetal alcoholisation syndrome – occurs following the consumption of very high quantities of alcohol. A certain amount of foetal damage can, however, be anticipated with a lower amount of consumption. Alcohol consumption equal to or greater than 20 g/day is associated with a reduced birth weight. Effects on the child's cognitive development have also been seen with a consumption of 20 g/day. From a theoretical standpoint, occasional excessive consumption at these critical stages may cause damage even if general alcohol consumption is low. The occasional, excessive consumption of at least 50 g/day during pregnancy has thus been associated with cognitive deficits.

It is difficult to define a threshold beyond which alcohol consumption would be risk-free to the foetus. In fact, the threshold values are based on group averages and there are intra- and interindividual variations in the pharmacokinetics of alcohol. Moreover, in view of the results obtained in laboratory animal models, there is no such thing as risk-free alcohol consumption during pregnancy. In order to prevent foetal exposure right at the start of pregnancy, excessive alcohol consumption should be avoided as soon as a pregnancy is planned.

Pathologies

Alcohol consumption significantly aggravates the advance of viral hepatitis. Subjects presenting with chronic infection due to the hepatitis B or C virus should be advised to drink alcohol only occasionally and not to excess. This information must be conveyed in particular to (former) drug addicts, who are especially prone to viral hepatitis.

Generally, patients with a liver disease (haemochromatosis – excessive iron content in the body, specific lesions observed after the pathological examination of the liver, obesity and alcoholic hepatitis, etc.) are particularly sensitive to the harmful effects of alcohol.

Some populations that take medications (with hepatotoxic potential) must be informed of the consequences of alcohol consumption. Paracetamol should therefore not be administered in cases of significant, chronic alcoholisation.

TO TAKE VULNERABILITY AND PROTECTION FACTORS INTO ACCOUNT IN INFORMATION AND

PREVENTION CAMPAIGNS

Individual genetic susceptibility to the effects of alcohol may be due to the existence of polymorphism of metabolism enzymes influencing alcohol consumption. Some subjects (50 % of Asians) present with a genetic deficiency combined with signs of alcohol intolerance ("Antabuse effect"). The presence of this allele could therefore protect against excessive alcohol consumption by having a dissuasive effect.

Some genetic polymorphisms (metabolism enzymes of ethanol and other genes) may affect diseases associated with excessive alcohol consumption and various cancers in particular.

Cardiovascular protection is also subject to individual variability of genetic origin. Studies have shown that the diminished risk was partly due to an increase in HDL-cholesterol levels (cardioprotective factor). This increase in HDL-cholesterol levels with moderate alcohol consumption is not routinely found in all populations, but is nevertheless significant in those with certain genetic polymorphisms.

Individual corpulence also impacts upon the effect of alcohol. Overweight subjects use the calories provided by alcohol intake more efficiently: they increase their weight whilst slim subjects tend to lose weight. Overweight subjects do not benefit from the protective effect of alcohol (no effect on HDL-cholesterol levels). Moreover, obesity associated with excessive alcohol consumption increases the risk of cirrhosis.

Finally, malnutrition, which has a specific impact on vitamin status, is susceptible to the effects of alcohol.

Research development

TO INVESTIGATE THE PHARMACOKINETIC VARIATIONS OF ETHANOL ACCORDING TO GENDER AND AGE IN DIFFERENT GROUPS OF SUBJECTS

Women are more sensitive than men to some of the toxic effects of alcohol, especially in so far as hepatotoxicity is concerned. Moreover, cardiovascular protective effects are evident in women following consumption of smaller quantities of alcohol compared with men. Given the reduced volume of distribution of ethanol in the female body, blood ethanol levels are higher following consumption of a similar quantity of alcohol. Recent studies refer to the reduced activity in women of an isoenzyme (χ-ADH) involved in the gastric metabolism of ethanol (first-pass effect). This diminished activity is evident for drinks containing 10 % or 40 % of ethanol. Thus ethanol blood levels are higher in women than in men following consumption of equivalent quantities of alcohol.

The pharmacokinetic profile of alcohol varies according to the pattern of consumption (on an empty stomach or with food). It is also influenced by the subject's age due to changes in the fat/lean mass distribution with age, which impacts differently upon blood ethanol levels in men and women. Between the ages of 25 and 60, the fat mass doubles in men and increases by 50% in women. Hormone status could also affect the pharmacokinetics of ethanol.

The expert group recommends investigating variations in the pharmacokinetics of alcohol according to gender (and weight), age and hormone status: young subjects (male and female) *versus* elderly subjects (male and female), menopausal women receiving hormone replacement therapy *versus* untreated menopausal women.

TO DEVELOP RESEARCH ON ALCOHOL INDUCTION OF CYP2E1 IN MAN, AND ITS REGULATION

Many laboratory animal studies have shown that CYP2E1 – the ethanol metabolism enzyme – is induced by chronic alcohol consumption and is involved in the liver toxicity of alcohol, notably via the production of reactive oxygen species. However, the induction of CYP2E1 in man under various conditions of consumption has scarcely been documented. What is the daily dose of alcohol that triggers induction? Does it depend on the quantity of alcohol ingested or on circulating levels of alcohol, the interindividual variations for the same quantity of alcohol ingested, and whether or not diet has a significant effect on this induction process (some foods have an inhibitory effect on CYP2E1)? The expert group advocates intensifying research into CYP2E1 regulation in man due to its involvement not only in the toxicity of alcohol, but also in that of certain medications (anaesthetics, paracetamol), or in the activation of procarcinogens (e.g. nitro amines) present in our environment.

On the other hand, the study in man of ethanol metabolism enzymes demands a straightforward assessment of their activity. As regards CYP2E1, a certain number of tests have been proposed (determination based on liver biopsies, *in-vivo* metabolism of chlorzoxazone used as a test substance), but these tests have constraints that limit their use. It has recently come to light that in man the RNA messenger level of CYP2E1, measured in the lymphocytes, was correlated to hepatic CYP2E1 activity. The expert group recommends that these tests be developed in lymphocytes in order to establish the level of CYP2E1 in man from a simple blood sample.

TO CARRY OUT RESEARCH ON THE MECHANISMS OF ADAPTATION TO OXIDATIVE STRESS

Oxidative stress appears to be a key pathogenic factor in hepatic lesions secondary to chronic alcoholisation. There are, however, various mechanisms for adapting to oxidative stress, which must play a role in the development and intensity of tissue lesions. The cell mechanisms of resistance to chronic oxidative stress include the induction of enzymes such as SOD-Mn (superoxide dismutase), thermal shock proteins (HSP...), apoptotic proteins (Bcl_2 and Bax), transcription factors (NFκB, AP_1...) and glutathione synthesis (GSH).

The expert group recommends the analysis of the mechanisms for adapting to oxidative stress and evaluation of the impact of factors such as polyunsaturated fatty acids and iron involved in the development of alcohol-related diseases. This type of studies initially requires an experimental alcoholisation model of the rat characterised by hepatic lesions similar to those observed in human alcoholism. The study will evaluate the systems for adapting to oxidative stress under various conditions during a blood alcohol cycle and in the hepatocytes of the periportal and perivenous zone. The studies will also investigate the effect of anti-oxidant substances at various stages in alcoholisation, either continuously or intermittently, by taking into account the fact that overloading with anti-oxidant substances may influence the systems involved in signal transduction.

In man, the results of studies focusing on the research into the characteristic signs of oxidative stress during alcohol-related liver diseases mostly corroborate this phenomenon. Moreover, the physiological increase in free-radical production with age can be potentiated by alcohol consumption, thus resulting in a marked pro-oxidant effect. This situation, which may be associated with malnutrition and inadequate intake of anti-oxidant agents, may also enhance the harmful effects of excessive alcohol consumption. Few studies have assessed the benefits of supplementing with several anti-oxidant agents with synergistic properties. According to the expert group, the effects of antioxidant agent supplementation (polyunsaturated phosphatidylcholines, S-adenosyl methionine, vitamin C...) on the

prognosis of alcohol-related diseases should be investigated.

TO DEVELOP BASIC RESEARCH ON THE ROLE OF CYTOKINES IN ALCOHOL-INDUCED LIVER DISEASE

Many experimental studies have confirmed the dominant role of cytokines in the pathogenesis of alcohol-related liver lesions. The animal modelling of alcohol-related liver disease must enhance basic and clinical research into alcohol-related liver diseases. The expert group recommends that links be forged between research units possessing expertise in the field of inflammation and clinical research centres specialising in alcohol-induced liver diseases in order to investigate the role of cytokines in lesion progression. These studies could explore the variation in the secretion of pro-inflammatory cytokines in relation with the oxidative stress and genetic polymorphisms (CD4, for instance) in conjunction with liver disease.

In terms of secondary prevention, it would be interesting to promote the introduction of randomised clinical trials to test the inhibition of pro-inflammatory cytokines in patients with severe forms of alcohol-induced liver disease.

TO USE EXISTING COHORTS TO MONITOR THE ONSET OF ALCOHOL-RELATED DISEASES AND TO DETERMINE THE CONCOMITANT RISK FACTORS

Various French cohorts (Suvimax, Gazel, E3N, Prime, Trois cités) are collecting data on cardiovascular morbidity and mortality, cancer (or all diseases) and dementia. Some of the data refer to alcohol consumption by the study participants and various laboratory specimens (DNA, serum, etc.) were collected at inclusion. The expert group recommends that these cohorts be strengthened and used so they provide information in future years relating to all diseases associated with excessive alcohol consumption.

The analysis of cohorts dedicated to the follow-up of cardiovascular diseases or cancers should give a better understanding of the natural history of these conditions occurring in conjunction with alcohol consumption, on concomitant risk factors and any interactions with other biological or environmental parameters: effect of the quantity consumed at the time of data collection and at different stages in life (around 10-15 years, 20 years, 30 years and 40 years), the effect of the duration of alcohol intoxication, the effect of stopping consumption (ex-consumer effect) and the type of alcohol consumed (wine, beer, cider or spirits); interactions with dietary habits, vitamin supplementation, hormone status (HRT (THS en français), menopause, etc.), corpulence and genetic polymorphism…

The follow-up of elderly subjects over 65 years of age should provide answers to any outstanding questions regarding the role of moderate alcohol consumption on cognitive functions and the risk of dementia (taking all causes into account or, more specifically, for vascular dementia or Alzheimer's disease). Although alcohol-mediated protection against dementia or cognitive deterioration has been confirmed in independent populations (and in countries consuming different types of alcoholic beverages), the impact of certain laboratory (high-density lipoproteins, coagulation or inflammation factors, polymorphisms of alcohol metabolism enzymes, etc.) or environmental parameters (extent of social interaction between subjects, etc.) has yet to be determined. The existence of a correlation between effects on cognitive functions and the doses consumed is of considerable relevance in these studies especially since the elderly populations, which, to date, have been involved in cognition studies, are seldom heavy drinkers of alcohol. Interpretation of the epidemiological studies

should be based on experimental data relating to the effects on the central nervous system of low but chronic alcohol consumption.

TO CARRY OUT STUDIES TO DETERMINE THE NATURAL HISTORY OF ALCOHOL-BASED LIVER DISEASES

There is a paucity of data regarding the organic consequences of excessive alcohol consumption, particularly with regard to alcohol-induced liver diseases. The expert group recommends the creation, in conjunction with existing structures, of an observatory for alcohol-related liver diseases involving the collection of diagnoses of alcohol-related liver disease and that of laboratory specimens. Data analysis should initially evaluate the real frequency of alcohol-related liver diseases. Furthermore, the duration of exposure required to induce a concomitant disease together with the life-time consumption period and the impact of stopping alcohol consumption on risk reduction could be investigated. Finally, interactions between the course of alcohol-induced liver disease and viral infection could be examined via serology and HBV in particular.

Regarding alcohol-induced liver disease, there is hardly any correlation between the clinical symptoms and the extent of liver involvement. The expert group recommends the introduction of a risk score combining clinical and laboratory items in order to identify, at an early stage, those consumers at risk of liver disease and those requiring liver biopsy to confirm the diagnosis.

TO DEVELOP SCREENING STRATEGIES TO DETECT ALCOHOL CONSUMPTION IN PREGNANT WOMEN, INCLUDING BIOLOGICAL MARKERS

The alcohol consumed by pregnant women easily crosses the placenta and its concentration is rapidly balanced between mother and child. Depending on the way in which the alcohol is consumed by the mother, her metabolic capacities and individual foetal sensitivity, a series of disruptions may be observed in a continuum ranging from minor behavioural disorders to a severe abnormal development manifested as "foetal alcoholisation syndrome" (or FAS, formerly known as foetal alcoholism syndrome) characterised by craniofacial dysmorphia, retarded growth and behavioural and cognitive handicaps.

In 1998, almost 4% of the women interviewed in maternity hospitals as part of the French national perinatal survey admitted to drinking at least one glass of alcohol per day during their pregnancy.

The expert group recommends that, within the scope of repeated cross-studies, alcohol consumption during pregnancy be routinely checked in maternity hospitals using questionnaires not only to document the frequency of consumption, but also to monitor its course. This control would benefit from the development of a simple and reliable biological marker of alcohol consumption.

In order to screen excessive alcohol consumers during prenatal visits, the validity of the questionnaires should be assessed in conjunction with laboratory assays and the impact of a management strategy should be evaluated. Occasional, excessive consumption, which can also adversely affect the child's development, should also be taken into account.

TO INVESTIGATE THE CONSEQUENCES OF *IN-UTERO* EXPOSURE IN TERMS OF BASIC, CLINICAL

AND EPIDEMIOLOGICAL RESEARCH

The effects on the child of exposure to doses lower than those triggering foetal alcoholisation syndrome are less well known, but certain studies have highlighted deficits in various areas: psychomotor development or intelligence and impaired learning, memory, attention or behavioural capacities. The expert group recommends that studies involving large cohorts be carried out to establish the effects of maternal alcohol consumption on the unborn child. The group suggests a more in-depth investigation of the relationship between the characteristics of maternal alcohol consumption (doses ingested, especially low doses, consumption patterns, exposure period and interactions with other factors such as smoking, etc.) and the deficit level of the child. Isolated results appear to indicate that excessive isolated consumption (at least 5 glasses at one time) during pregnancy are likely to trigger intellectual deficits in the child. There are also arguments that postulate a teratogenic risk in children whose fathers drink alcohol to excess, but not enough studies have been carried out yet on this particular topic.

According to laboratory animal experiments, alcohol absorption is harmful throughout pregnancy and no threshold dose under which there is no risk to the offspring has ever been established. The expert group recommends encouraging studies focusing on the regulation of genes controlling cerebral development. Such studies might, perhaps, identify predictive biochemical markers of specific lesions (proteins - the expression of which is stimulated or suppressed at a given time), especially in risk patients.

The expert group recommends evaluating the treatments (anti-oxidant substances and growth factors) aimed at countering the *in-utero* and post-natal effects of alcohol. To this end, the stages of pregnancy during which certain mechanisms (possibly the target of a specific pharmacological intervention) may be chiefly involved should be identified.

Studies conducted in rats have shown a good correlation between cerebral, anatomical involvement and neurological deficits observed following *in-utero* exposure to alcohol. Similarly, lesions affecting the principal structure (hippocampus) involved in learning and memory processes and a reduction in the size of the cerebellum have been reported in children whose mothers consumed alcohol throughout pregnancy. These observations might explain the cognitive problems and the motor development disorders observed in these children. The expert group therefore recommends that clinical trials involving children presenting with foetal alcoholisation syndrome should include imaging techniques.

Greater understanding of the process of cerebral plasticity should enable the effects of stimulation via an "enriched environment" on cerebral plasticity to be assessed in children suffering from FAS to varying degree.

TO INVESTIGATE THE MECHANISMS OF NEURONAL DEFICIT DURING EXCESSIVE ALCOHOL CONSUMPTION AND THE POTENTIAL REVERSIBILITY OF THE LESIONS OBSERVED

A high alcohol consumption triggers the onset of cognitive disorders affecting almost half of heavy drinkers. The ensuing damage is serious but, nevertheless, is largely reversible, including the principal phenomenon of this condition, Korsakoff syndrome. These effects could therefore be subjected to a specific management approach. However, many questions are still outstanding. We do not know, for instance, why certain users are apparently symptom –free despite a high alcohol consumption whilst others are affected at an early stage. According to the expert group, studies should be carried out in an attempt to establish the correlation between the dose, the period of consumption and the effects observed. Most of the studies to date have been carried out in situations accommodating excessive

consumers but the results of some studies suggest that the cognitive disorders could be observed with a more moderate consumption. Future studies should endeavour to specify this risk threshold. As for other alcohol-related diseases, the role of the consumption pattern, whether occasional or constant, could also be investigated. Furthermore, discrepancies between the significance of functional modifications and the results of cerebral imaging have also been observed. Studies focusing more specifically on the anatomy of cognitive disorders would prove useful.

Once the existence of cognitive disorders associated with excessive alcohol consumption has been demonstrated, the second step must consist in investigating ways of reversing the condition. The mechanism of alcohol neurotoxicity has not been fully elucidated. Many effects have been observed, especially in cells, but their respective clinical role has yet to be specified. The simplest hypothesis, namely that of neuronal destruction, has only been partly confirmed. In fact, other processes are involved, as indicated by the re-expansion of the volume of the encephalon in users who have stopped alcohol consumption. The expert group recommends that the mechanisms involved in the reversibility of effects be investigated in studies focusing in particular on current imaging developments. Although it has been demonstrated that the disorders can actually be reversed, the chronological sequence of this process is still extremely imprecise since it is measured in weeks or years, depending on the authors. Similarly, the nature of the factors playing a prognostic role is not known. The differences that really appear to exist between Korsakoff syndrome and other cognitive disorders should be taken into account. These studies could the therapeutic strategies that must be developed in this area.

The onset of neurological disorders, which is sometimes very fast, suggests that mechanisms other than those due to the direct toxicity of alcohol may be involved. The role of thiamine deficiency in the occurrence of a Wernicke-Korsakoff's syndrome has now been established, but the exact origin of this deficiency (low intake or poor absorption?) and its mechanism of action have not been clarified. According to the expert group, the role of depleted enzyme activity of genetic origin should be explored within the scope of thiamine deficiency. Intervention studies should also investigate the practical possibility of preventing the syndrome by means of vitamin B1 administration. Lastly, the likely involvement of other mechanisms such as the processes of excitotoxicity associated with the withdrawal syndrome, must be investigated in experimental and clinical studies.

TO CONTINUE AND DEVELOP RESEARCH ON GENETIC SUSCEPTIBILITY TO THE EFFECTS OF ALCOHOL

The onset of organic complications during excessive alcohol consumption is influenced by genetic polymorphisms and ethanol metabolism enzymes in particular (ADH, ALDH, CYP2E1). Most of the studies carried out on these enzymes have focused on the regulation and expression of ADH genes. More recent studies have investigated the genetic polymorphisms of ALDH (the muted ALDH2 allele in particular, found in 50% of the Asian population) and CYP2E1. The expert group recommends that investigations should be encouraged in this area with studies including a large cohort (given the rarity of certain polymorphisms), studies involving comparison of healthy excessive consumers and excessive consumers presenting with disease. These investigations using "genome scanning" and/or "candidate genes" techniques should take into account the gene/gene interactions caused by the probably polygenic aspect of individual vulnerability. A bank of laboratory specimens (DNA, serum) obtained from persons presenting with excessive consumption must be created in advance. The information provided by these studies should help to assess

the effect of the various polymorphisms on the level of individual alcohol consumption and on the development of diseases associated with excessive alcohol consumption. Vulnerability thresholds relating to the development of an alcohol-related disease could also be determined according to genotypes.

TO STUDY THE EFFECT OF THE PATTERNS OF ALCOHOL CONSUMPTION ON THE DEVELOPMENT OF VARIOUS DISEASES AND ON CORPULENCE

Alcoholisation patterns (type of beverage, regularity/irregularity of consumption, with or without food, occasional, excessive consumption, etc.) are a parameter for consideration when assessing the onset of alcohol-related effects. The risk of cerebrovascular accident, for example, is known to be greater following an acute excessive alcohol consumption. Moreover, the pattern of consumption could influence the lipid profile. Moderate, regular consumption would increase HDL levels whilst irregular, excessive consumption would be associated with an unfavourable lipid profile. Laboratory animal studies have shown that the harmful consequences of alcohol exposure can vary according to the pattern of maternal alcoholisation and that isolated excessive consumption by pregnant women can cause harmful effects in the unborn child. The expert group recommends that the consumption pattern be routinely documented in future epidemiological studies.

In individuals who consume alcohol, weight should tend to increase due to the intake of additional calories, the energy value of alcohol being 7.1 kcal/g. Observational, essentially North-American, studies have, on the whole, shown that although alcohol consumption is, in fact, associated with weight gain in man, this weight gain is less than that anticipated or occurs irregularly. In women, the relationship would be reversed, corpulence markers generally being lower in alcohol consumers than in non-consumers. This latter observation was, not, however corroborated in an Italian study in which women drinking wine were consistently stouter than their abstaining counterparts. Alcohol intake in man has been shown to promote abdominal obesity, particularly when accompanied by a sedentary lifestyle and a diet rich in lipids. It is important to point out that the relationship between alcohol consumption and corpulence can be influenced by the methods of consumption, which would account for the differences observed from one country to the next. The expert group recommends that prospective studies of interactions between alcohol consumption and corpulence be conducted in France, taking consumption patterns and confounding factors into account.